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REVIEW ARTICLE

The efficacy of probiotics in experimental autoimmune encephalomyelitis (an animal model for MS): a systematic review and meta-analysis

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Multiple sclerosis (MS) is an autoimmune disease, and its treatment is a challenge for the researcher. One of the options for treating this disease is the use of different probiotics, so we tried to review and analyse the results of researches that used probiotics for the treatment of Experimental autoimmune encephalomyelitis (an animal model for MS). The effectiveness of probiotics in the treatment and improvement of MS can make a big difference in the life quality of patients.

Keywords
association, experimental autoimmune encephalomyelitis, meta-analysis, multiple sclerosis, probiotics.

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Abstract

Probiotics immunomodulatory properties and their beneficial effects for diseases such as multiple sclerosis (MS) are reported by several studies. The current systematic review and meta-analysis aimed to investigate the favourable effects of probiotics in improving experimental autoimmune/allergic encephalomyelitis (EAE) as an animal model of MS. We systematically searched Scopus, Web of Sciences (ISI), and PubMed databases to identify relevant studies from the inception of these databases to December 2019. A total of 15 animal studies met the inclusion criteria, while no human study met the inclusion criteria. The association between consumption of probiotics and each sign was calculated using the producing pooled odd ratios (95% confidence interval [95% CI]) in a random effect model. The meta-analysis revealed the significant effect of probiotics on the incidence of EAE, weight gain, and clinical symptoms. However, the effects of probiotics on the duration of the disease varied by probiotic strain. The administration of probiotics was associated with a significant reduction in the risk of mortality only in female animals. Moreover, the meta-analysis revealed the promising effects of probiotics on the prevention and management of EAE.

Introduction

Autoimmune diseases (ADs) are believed to arise from uncontrolled responses to endogenous antigens and a defect in immune regulation. Therefore, self-reactive T cells play a crucial role in their incidence (Berkovich 2019). Multiple sclerosis (MS) is one of the most common autoimmune and chronic diseases of the central nervous system (CNS) that is

a major cause of work disability (Abdurasulova *et al*. 2017). The MS develops due to the destruction of myelin sheaths of the CNS and is characterized by damage to oligodendrocyte (cells that produce myelin) and neurons and their axons, astrogliosis, inflammatory lesions, and impairment of Blood-brain barrier integrity (BBB) in young people (Lassmann *et al*. 2012). Mobility, sensation, sphincter function, cognition, and function difficulties are inevitable complaints of individuals with MS (Brownlee *et al*. 2017). Although the exact aetiology and pathogenesis of MS are not fully understood, it is believed that both environmental and genetic factors trigger the disease to start (Mielcarz and Kasper 2015). MS is generally considered a $CD4^+$ T-cell-mediated disease. However, other types of immune cells (e.g., CD^+ T-cell, B-cells, natural killer [NK], and macrophages) and glial cells (including microglia and astrocyte) play a role in the disease development (Høglund and Maghazachi 2014). Furthermore, dysbiosis and other gastrointestinal tract disorders have been demonstrated to influence MS (Levinthal et al. 2013; Preziosi *et al*. 2013). It is worth noting that experimental autoimmune/allergic encephalomyelitis (EAE) is one of the most commonly used experimental animal models to investigate different aspects of MS.

It is better to mention that there is some difference between MS and EAE. The main difference is the need for external immunization to induce EAE (Gran *et al*. 2007). Also, unlike EAE, MS-inducing antigens have not been identified.

According to the definition of FAO/WHO, *probiotics are living microorganisms that, when administered in adequate amounts*, have beneficial health effects for the host. Numerous beneficial effects have been identified for probiotics, which improve the host's health status by improving the intestinal environment and affecting the immune system function (Miyazaki 2015; Nishihira *et al*. 2016). Several studies reported that probiotics might be able to help to prevent and treat a wide range of allergic and chronic ADs (Gill and Guarner 2004; Tlaskalová-Hogenová *et al*. 2004), particularly managing the severity of EAE (Kobayashi *et al*. 2010; Lavasani *et al*. 2010; Takata *et al*. 2011; Kwon *et al*. 2013). The current systematic review and meta-analysis aimed to evaluate the efficacy of probiotics consumption in the management of EAE (MS in animal models).

Results and discussion

The study selection process resulted in 168 articles. After reviewing the titles or abstracts, 128 articles were excluded due to not having inclusion criteria. Forty remaining articles were thoroughly reviewed. After a full-text review, 25 articles were discarded. Eventually, 15 studies had the inclusion criteria and were selected for the meta-analysis (Maassen *et al*. 1998, 2003; Baken *et al*. 2006; Ezendam *et al*. 2008; Ezendam and van Loveren 2008; Kobayashi *et al*. 2010; Lavasani *et al*. 2010; Takata *et al*. 2011; Kobayashi *et al*. 2012; Kwon *et al*. 2013; Abdurasulova *et al*. 2016a; Abdurasulova *et al*. 2016b; Salehipour *et al*. 2017; Secher *et al*. 2017; Consonni *et al*. 2018; Libbey *et al*. 2018; Yamashita *et al*. 2018; He *et al*. 2019). It should be mentioned, in some of the selected studies, more than one probiotic bacterium or animal species have been examined, so 25 dependent subgroups were obtained from 15 studies. All selected articles were animal experiments. The general characteristics of the included studies are shown in Table 1. In all included studies, after EAE induction, all or some of the following variables are compared between the probiotic and control groups, including incidence, onset, and duration of the disease, mortality, weight change, and maximum clinical score.

As mentioned in Table 1, different methods have been used in different studies to induce the EAE. Considering that we used the difference in the results of each factor between the two groups in each study, so this difference in the method of induction of EAE does not affect the analysis because a certain method was for both of control and probiotic groups in each study.

Based on the results of the meta-analysis, the incidence of EAE was significantly lower in mice treated with probiotics (SMD, 0·90; 95% CI, 0·83–0·96; $I^2 = 31·6\%$) (Fig. 1a). Besides, they had a significant delay in EAE onset (SMD, 0·51; 95% CI, 0·29–0·72; $I^2 = 18·5\%$) (Fig. 1b). The results of the subgroup analysis, based on the probiotic type, showed that use of *Enterococci* was associated with a significantly shorter duration of EAE (SMD −0·75, 95% CI −1·16 to −0·35; $I^2 = 0·0\%$), while the use of other probiotics was not associated with a significant effect on the EAE duration (Fig. 2a).

In the subgroup analysis, based on the rate of mortality, the meta-analysis showed that the use of probiotics could significantly reduce the risk of mortality in treated mice compared with controls (OR, 0·01; 95% CI, 0·01–0·3; $I^2 = 0·0\%$), although this reduced risk of mortality was only significant in females (OR, 0·05; 95% CI, 0·01–0·2 for females and OR, 1·00; 95% CI, 0·24–4·09 for males) (Fig. 2b). Analyses performed on the weight showed that the treatment group had a significantly higher mean weight than the control group (SMD 0·18, 95% CI −0·23 to 0·59) (Fig. 3a). The results also revealed that mice in the treated group had a significantly lower score for clinical symptoms than controls (SMD −0·88, 95% CI −1·20 to −0·57) (Fig. 3b). Meta-regression analysis showed a significant decrease in treated mice's clinical symptoms than the controls (Coefficient $[C] = -0·0997$; $P = 0·02$). Heterogeneities in all analyses were acceptable. Also, Egger's tests revealed no publication bias (Fig. 4).

Table 1 Summary of animal experiment studies on the efficacy of probiotics in EAE (F = female, M: male, B: both male and female)

Author	Country, year	Probiotic	Animal (sex)	Probiotic group number	Control group number	Intervention period (after EAE induction)	EAE model	Analysed parameters
Abdurasulova *et al*.	Russia, 2016	*Enterococcus faecium strain L-3*	Rat (B)	26	35	28	Encephalitogenic mixture (EGM)	Incidence, onset, duration, clinical score
Abdurasulova *et al*.	Russia, 2017	*Enterococcus faecium strain L-3*	Rat (B)	20	20	28	EGM	Incidence, Onset, Duration, Mortality, Clinical score
Baken *et al*.	Netherlands, 2006	*Lactobacillus casei Shirota*	Rat (B)	8	7	28	Guinea pig myelin basic protein (MBP)	Incidence, Duration, Mean weight, Clinical score
Ezendam *et al*. (A)	Netherlan, 2008	*Lactobacillus casei Shirota*	Rat (M)	8	8	27	MBP	Incidence, Onset, Duration, Clinical score
			Rat (F)	8	8			Incidence, Onset, Duration, Clinical score
Ezendam *et al*. (B)	Netherland, 2008	*Bifidobacterium animalis*	Rat (F)	4	4	27	MBP	Incidence, Onset, Duration, Clinical score
			Rat (M)	4	4			Incidence, Onset, Duration, Clinical score
He *et al*.	USA, 2019	*Lactobacillus reuteri strain 17938*	Mouse (B)	40	37	20	Myelin oligodendrocyte glycoprotein peptide (MOG)	Incidence
Kobayash *et al*.	Japan, 2010	*Lactobacillus casei strain Shirota*	Rat (M)	8	8	28	MBP	Incidence, Onset, Duration, Mortality
			Rat (F)	8	8			Incidence, Onset, Duration, Mortality
		Bifidobacteria breve strain Yakult	Rat (M)	8	8			Incidence, Onset, Duration, Mortality
			Rat (F)	8	8			Incidence, Onset, Duration, Mortality
Kobayash *et al*.	Japan, 2012	*Lactobacillus casei strain Shirota*	Mouse SJR (F)	14	14	49	Proteolipid Protein (PLP)	Mortality, Clinical score
			Mouse C57 (F)	12	12	28		Clinical score
Kwan *et al*.	South Korea, 2013	IRT5 probiotics (*Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus reuteni, Bifidobacterium bifidum, and Streptococcus thermophiles*)	Mouse C57 (B)	30	30	49	MOG	Incidence, Clinical score
Libbey *et al*.	USA, 2018	*Lactobacillus paracasei, subspecies paracasei*	Mouse (B)	15	13	16	MOG	Mean weight, Clinical score

(continued)

Table 1 (continued)

Author	Country, year	Probiotic	Animal (sex)	Probiotic group number	Control group number	Intervention period (after EAE induction)	EAE model	Analysed parameters
Massen *et al*.	The Netherland, 2003	Recombinant *lactobacilli* (*Lactobacillus casei*)	Rat (B)	13	9	20	MBP	Incidence
Salehipour *et al*.	Iran, 2017	*Lactobacillus plantarum* A7 and *Bifidobacterium animalis* PTCC 1631	Mouse C57	8	9	22	MOG	Incidence, Onset, Mean weight, Clinical score
		Lactobacillus plantarum A7		8	9			Incidence, Onset, Mean weight, Clinical score
		Bifidobacterium animalis PTCC 1631		8	8			Incidence, Onset, Mean weight, Clinical score
Secher *et al*.	France, 2017	*Escherichia coli* (strain MG1655)	Mouse C57	30	30	30	MOG	Incidence, Onset, Mortality, Clinical score
		Escherichia coli (strain nissle 1917)	Mouse C57	40	40			Incidence, Onset, Mortality, Clinical score
Takata *et al*.	Japan, 2011	*Pediococcus acidilactici* R037	Mouse C57	17	18	21	MOG	Incidence, Onset, Clinical score
			Mouse SJR	17	16			Incidence, Onset, Clinical score
Yamashita *et al*.	Japan, 2018	*Lactobacillus helveticus SBT2171*	Mouse SJR (F)	10	10	42	PLP	Incidence, Clinical score

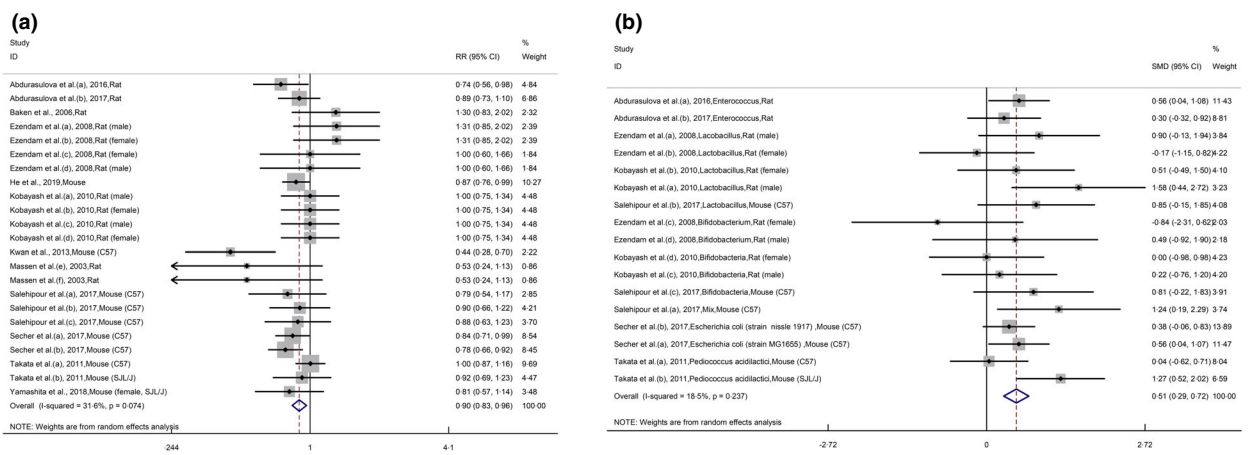

Figure 1 (a) Analysis for risk of incidence of EAE in the probiotic group compared with the control group, (b) Analysis for risk of the onset of EAE in the probiotic group compared with the control group.

To the best of our knowledge, this study is the first systematic review, meta-analysis study on the effect of probiotic bacteria on the clinical condition of EAE. In recent years, some studies have investigated the effect of probiotics on the clinical status of EAE and have reported various effects, which in general are promising. The results

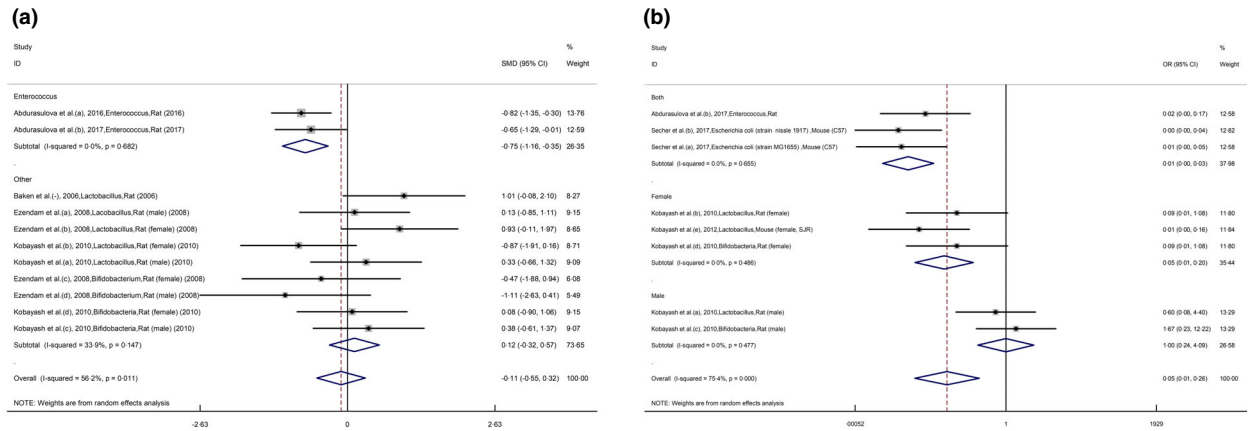

Figure 2 (a) Analysis for risk of the duration of EAE in the probiotic group compared with the control group, (b) Analysis for risk of mortality chances in the probiotic group compared with the control group.

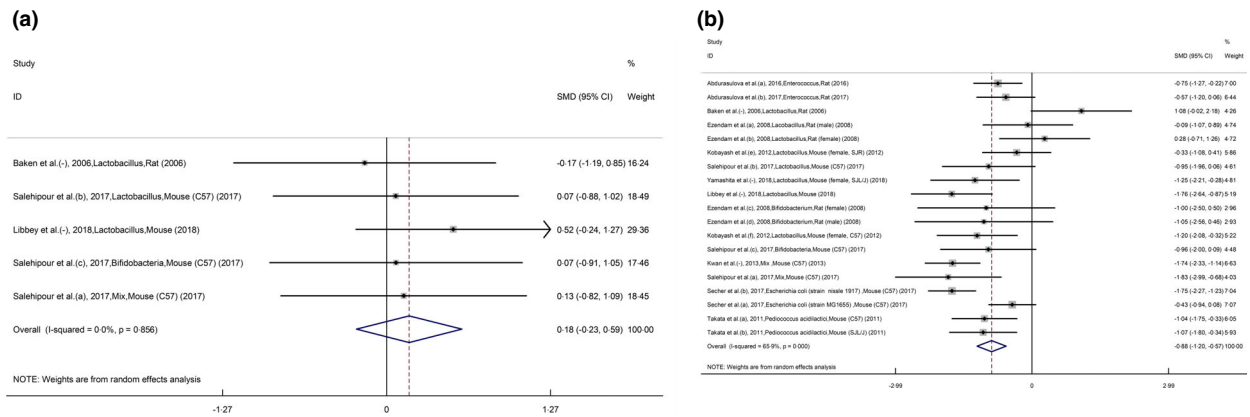

Figure 3 (a) Analysis for risk of incidence of mean weight in the probiotic group compared with the control group. (b) Analysis for risk maximum clinical score of EAE in the probiotic group compared with the control group.

indicated that, in animals, consumption of some strains of probiotics could ameliorate EAE. Therefore, the authors suggest investigating its efficacy for human use. Such results are reported by other similar meta-analysis studies, which claimed that probiotic administration is associated with the clinical condition of some other autoimmune ulcerative colitis (UC) (Derwa *et al.* 2017). However, some meta-analysis studies reported no beneficial effect for the administration of probiotics on the management of autoimmune disorders, such as rheumatoid arthritis and Crohn's disease (CD) (Derwa *et al.* 2017; Mohammed *et al.* 2017). Results of subgroup analysis revealed that the effect of probiotics on some clinical parameters of EAE might depend on the genus of bacteria. Nevertheless, unlike other probiotics, *Enterococci* bacteria could significantly reduce the duration of EAE.

Concerning the association between probiotics consumption and EAE incidence (risk to the development of EAE), 23 eligible sub-studies were obtained from 13 studies (Maassen *et al.* 2003; Baken *et al.* 2006; Ezendam *et al.* 2008; Ezendam and van Loveren 2008; Kobayashi *et al.* 2010; Takata *et al.* 2011; Kwon *et al.* 2013; Abdurasulova *et al.* 2016b; Abdurasulova *et al.* 2017; Salehipour *et al.* 2017; Secher *et al.* 2017; Yamashita *et al.* 2018; He *et al.* 2019). Based on the findings, the relative risk of EAE incidence is 10% lower among those who receive probiotics than in the control group, which indicates the potential role of probiotics consumption in preventing EAE.

Concerning the onset of the EAE, we could extract data of 20 groups from identified studies (Baken *et al.* 2006; Ezendam *et al.* 2008; Ezendam and van Loveren 2008; Kobayashi *et al.* 2010; Takata *et al.* 2011; Abdurasulova *et al.* 2016b; Abdurasulova *et al.* 2017; Salehipour *et al.* 2017; Secher *et al.* 2017; Consonni *et al.* 2018; Yamashita *et al.* 2018). The reported results were controversial; for example, in Takata *et al.* (2011) study, unlike C57BL/6

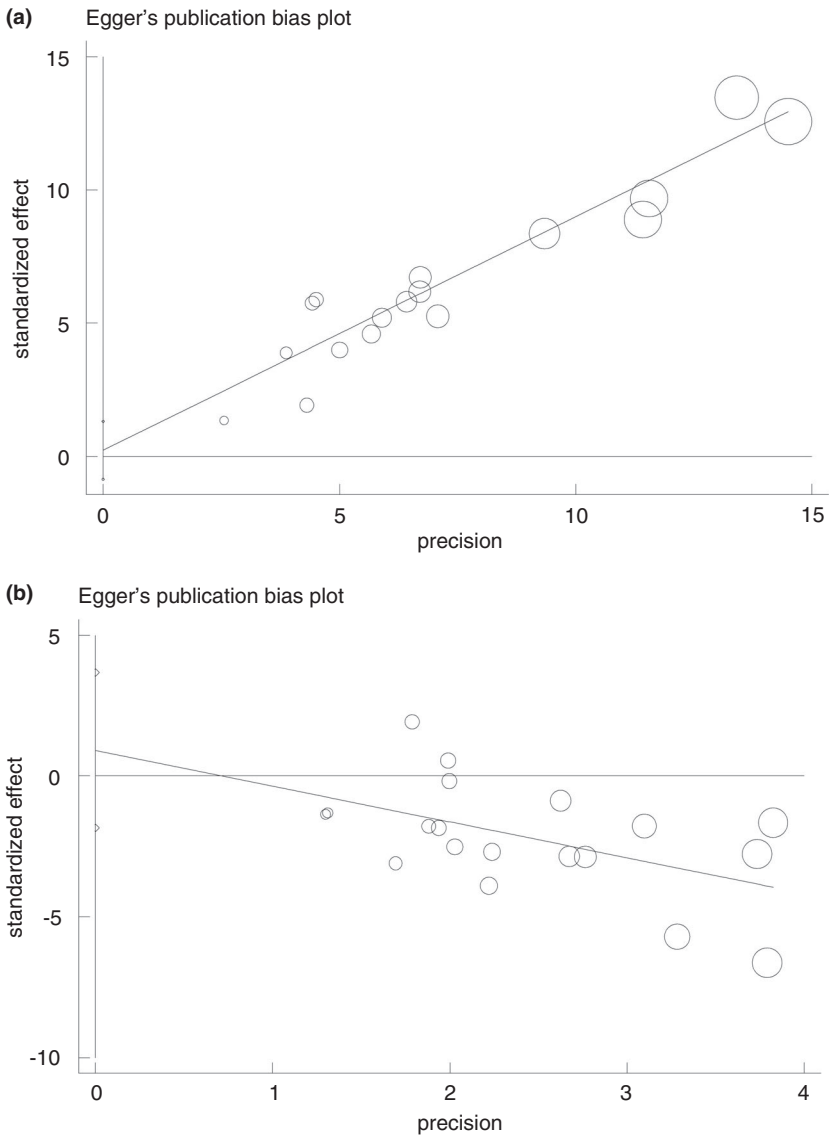

Figure 4 Publication bias using Egger's plot according to data of incidence of EAE (a), and the maximum clinical score of EAE (b).

mice, delay of clinical manifestation onset was found significant for SJL/J mice. However, the overall result of our analysis revealed that the administration of probiotics could significantly delay the onset of EAE.

For the duration of the disease, only data of 11 independent groups were extracted from six studies (Baken *et al.* 2006; Ezendam *et al.* 2008; Ezendam and van Loveren 2008; Kobayashi *et al.* 2010; Abdurasulova *et al.* 2016b; Abdurasulova *et al.* 2017). According to our analysis, the outcome varied based on the probiotic strain. Of these studies, only two (Abdurasulova *et al.* 2016b; Abdurasulova *et al.* 2017) were used *Enterococci* bacteria, that both studies reported a significant association between probiotic consumption and decreased duration of the disease.

Data from four studies were used to analyse the association between probiotic administration and mortality rate of EAE (Kobayashi *et al.* 2010, 2012; Abdurasulova *et al.* 2017; Secher *et al.* 2017). According to gender and species or strain of animal and species or strain of probiotic, data of eight independent groups were extracted. The results of the meta-analysis indicated that probiotics could significantly decrease the risk of mortality only in females. These findings may have been limited by the small number of studies in each subgroup.

Concerning the analysis of the association between probiotic consumption and weight change, data of three studies were extracted, which in total included five groups (Baken *et al.* 2006; Salehipour *et al.* 2017; Libbey *et al.*

2018). Of these studies, only in one study, the association between probiotic use and weight gain was nonsignificant (Libbey *et al.* 2018).

The severity of symptoms directly impacts patients' quality of life, so we analysed the association between probiotic use and mean clinical score. We used data of 19 independent groups for this analysis that were extracted from 12 studies (Baken *et al.* 2006; Ezendam *et al.* 2008; Ezendam and van Loveren 2008; Takata *et al.* 2011; Kobayashi *et al.* 2012; Kwon *et al.* 2013; Abdurasulova *et al.* 2016b; Abdurasulova *et al.* 2017; Salehipour *et al.* 2017; Secher *et al.* 2017; Libbey *et al.* 2018; Yamashita *et al.* 2018). Unlike 12 cases, in seven cases, no significant association is found between the administration of probiotics and decreased clinical symptoms; also, the meta-analysis indicated that animals in the treated group had a significantly lower score for clinical symptoms than the controls.

The results of this meta-analysis suggested that probiotics may be helpful in preventing and managing EAE. It is worth noting that we could not find any eligible human study, so only animal experiments are reviewed. In fact, clinical trials do exist, but these were not considered for meta-analyses because of the lack of inclusion criteria chosen for the analysis. Also, one of the main limitations of this study is the short study period of included researches (mostly 21–70 days). So, the long-term effects of probiotics were not investigated.

Materials and methods

This systematic review and meta-analysis study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher *et al.* 2015; Fig. 5).

Search strategy and selection of articles

For the literature review, on December 13, 2019, two independent reviewers (A.B. and K.M.) systematically searched the Web of Sciences, PubMed/MEDLINE, and Scopus databases to identify all animal experiments and human clinical trial studies that were investigated the effect of probiotics consumption on the clinical status of EAE. No time or language restriction was applied. The review was conducted using the following core terms: (i) MS, experimental autoimmune encephalomyelitis, experimental allergic encephalomyelitis; (ii) probiotic, probiotics, Lactobacillus, Lactobacilli, Bifidobacterium, Bifidobacteria, Streptococcus, fermented milk, with employing the Boolean operators 'OR' and/or 'AND'. After removing duplications, the reviewers independently screened the titles and abstracts of identified studies for eligibility. Then, full texts of potentially relevant articles were evaluated in-depth. Disagreements were resolved through discussion or consultation of the third reviewer (S.A.).

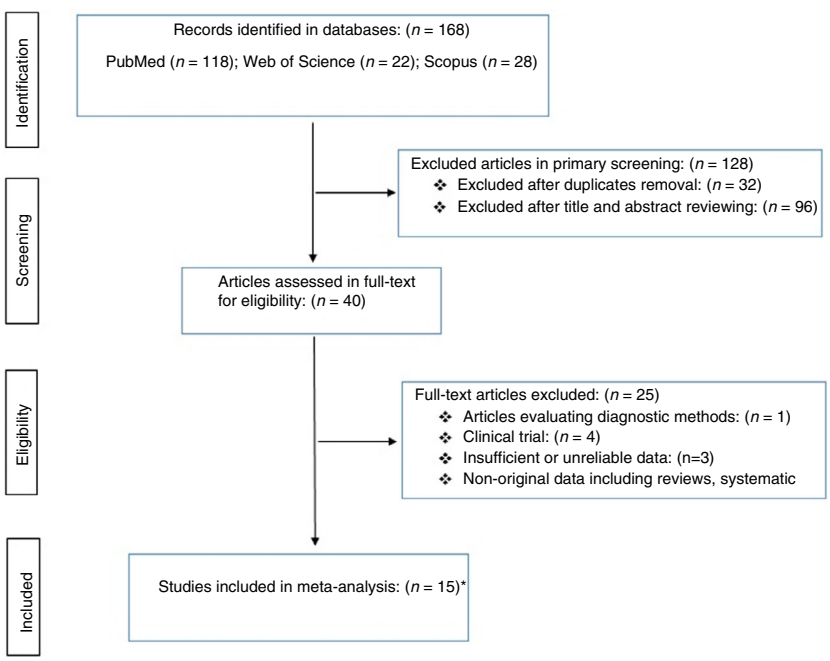

Figure 5 PRISMA flow chart showing the process of study selection.

In the present meta-analysis, the primary outcome of interest was the efficacy of probiotics, compared with the placebo in amelioration of EAE. Inclusion criteria were as follows: (i) peer-reviewed original animal experiments; (ii) studies with acceptable criteria for EAE scoring; (iii) published in English. Nonoriginal articles (i.e., editorials, letters, reviews, and systematic reviews), studies without a control group, clinical trials, and mechanism studies were excluded. It worth noting that we tried to use clinical trials for separate meta-analysis, but most of the retrieved meta-analyses did not have quantitative and consistent data.

Data extraction and study quality assessment

At first, a specific form was designed (by S.A.) in an Excel sheet to collect data. Data were extracted by two independent reviewers (H.B. and S.V). The collected data included author's name, publication year, country, study days after EAE induction, type (rat or mouse) and age of the animal at the beginning of the study, used material for EAE induction and its dose, probiotic bacteria, sample size, and outcomes of EAE (including incidence, onset, and duration of the disease, mortality, weight change, and maximum clinical score in the both of control and treatment groups). Discrepancies were resolved through discussion or, if necessary, consulting the third reviewer. The quality of studies was assessed using the Joanna Briggs Institute (JBI) (Institute 2017).

Data synthesis and Statistical analysis

Statistical analyses were performed using Stata software version 12 (Stata Corp.). The association between probiotics consumption and EAE amelioration was evaluated by producing pooled odd ratios and 95% confidence interval (95% CI) using the random effect model. *Q*-test and I^2 methods were used to assess the heterogeneity between studies. We considered the I^2 value of ≤25%, 50%, and 75% as low, medium, and high heterogeneity, respectively. Egger's publication bias method for asymmetry was used to detect publication bias. A *P*-value of <0·01 was considered statistically significant. Forest plots demonstrating OR's and 95% CI's were employed to indicate a possible correlation between probiotics consumption and EAE amelioration.

Conflict of Interest

There is no conflict of interest in this study.

Author contributions

Sepideh Abbaszadeh and Hamed Behniafar designed the study and collaborated to the manuscript writing. Ali Bahadori and Khalil Maleki Chollou collaborated in the search of articles. Hamed Behniafar and Soghra Valizadeh have extracted data. Seyed Mohammad Riahi and Soghra Valizadeh performed the statistical analysis and has analysed the data; Seyed Mohammad Riahi and Sepideh Abbaszadeh have critically reviewed the manuscript. The manuscript has been read and approved by all the authors. As stated earlier in this document, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

Data Availability Statement

The datasets collected during and analysed during this study are available from the corresponding author on reasonable request.

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