Archives of Oral Biology 83 (2017) 187–192

Contents lists available at ScienceDirect

Archives of Oral Biology

journal homepage: www.elsevier.com/locate/archoralbio

Review

A *meta*-analysis of randomized trials assessing the effects of probiotic preparations on oral candidiasis in the elderly

Ruixue Ai, Jiao Wei, Danhua Ma, Lu Jiang, Hongxia Dan, Yu Zhou*, Ning Ji*, Xin Zeng, Qianming Chen

State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu, Sichuan, China

ARTICLE INFO

Keywords:
Candidiasis
meta-analysis
Probiotic

ABSTRACT

Objective: Oral candidiasis is the most common fungal infection and can be attributed in part to dysbiosis, an imbalance in the resident oral microflora. Therefore, probiotics, which counter pathogenic microorganisms through competitive, antagonistic, and immunological effects, have been used by some clinicians. To date, the effect of probiotics in preventing oral candidiasis in the elderly is controversial. A systematic review that summarizes and critically appraises the available clinical trials is therefore necessary.

Design: Electronic searches were performed using the Pubmed, Embase, and Cochrane databases. Only randomized controlled trials were included. The Mantel–Haenszel test was used to appraise the odds ratio for single studies and an overall combined odds ratio for all studies combined.

Results: Three studies matched the inclusion criteria and were homogeneous. The data from one study that estimated candida growth from plaque and saliva were subdivided, thus a total of four studies with 595 people were included. The overall combined odds ratio was 0.54 (95% CI: 0.38–0.77). Three studies provided that active treatment reduced the risk of oral candidiasis more than placebo: Hatakka et al. (OR 0.51, 95% CI 0.26 to 0.97; 192 participants, plaque); Kraft-Bodi et al. (OR 0.46, 95% CI 0.24 to 0.86; 174 participants, palatal); Kraft-Bodi et al. (OR 0.50, 95% CI 0.26 to 0.98; 174 participants, plaque), while one study provided reverse result: Ishikawa et al. (OR 1.24, 95% CI 0.48 to 3.58; 55 participants, saliva).

Conclusion: Probiotics have a preventative effect on oral candidiasis in the elderly.

1. Introduction

The incidence of oral candidiasis, caused by a commensal and opportunistic pathogenic fungus, called candida, has escalated markedly in recent years, especially in the elderly population (Williams & Lewis, 2011). Oral candidiasis, which is attributed in part to dysbiosis, accounts for a major proportion of fungal infections found in the oral cavity (Coronado-Castellote & Jimenez-Soriano, 2013). A review of different techniques for diagnosis of oral candidiasis reported a dysbiosis prevalence in at least 87% of oral candidiasis cases (Coronado-Castellote & Jimenez-Soriano, 2013). Oral dysbiosis mostly results from the use of medicine, such as broad-spectrum antibiotics and immunosuppressive agents, while systemic disease, such as diabetes and malignancies, age (children or the elderly), and AIDS are other systemic factors (Lalla, Patton, & Dongari-Bagtzoglou, 2013; Patil, Rao, Majumdar, & Anil, 2015). Overgrowth of candida in the oral cavity can lead to local discomfort, such as burning pain and altered taste sensation. More seriously, if the infection spreads through the bloodstream or upper gastrointestinal tract in immune-compromised patients, infection can lead to significant morbidity and mortality (Akpan & Morgan, 2002).

To date, systemic and local antifungal agents have proven to be successful in preventing mucosal and invasive fungal infections. However, antifungal drugs have marked side effects, such as hepatic and renal toxicity, nausea, vomiting, and diarrhea (Oliver, Dhaliwal, Theaker, & Pemberton, 2004). The unpleasant taste of nystatin is also a drawback. Furthermore, the increased number of resistant strains and antifungal prophylaxis remains problematic (Sardi, Almeida, & Mendes Giannini, 2011; Sardi, Scorzoni, Bernardi, Fusco-Almeida, & Mendes Giannini, 2013). As elderly individuals are usually weak and wear dentures, oral candidiasis frequently recurs or is chronic. Thus, agents with low toxicity or no side effects, and effective against candida are needed (Pfaller, 2012).

Probiotics, the vast numbers of microorganisms dwelling in the

* Corresponding authors.
E-mail addresses: zhouyu19830306@sina.com (Y. Zhou), 32405973@qq.com (N. Ji).

http://dx.doi.org/10.1016/j.archoralbio.2017.04.030
Received 28 October 2016; Received in revised form 6 April 2017; Accepted 26 April 2017

mucous membrane of the host, are safe and beneficial to the host (Cremonini et al., 2002). The definition of probiotics in this study was somewhat vague, since it comprises different species with different characteristics. The most commonly used probiotic material is yogurt (Fisberg & Machado, 2015), which is generally used in daily life (Sanders, 2008). *Lactobacilli (L. rhamnosus HS 111, L. acidophilus HS101)* and bifidobacteria, termed "bifidus", are the species most commonly used as probiotics (Saarela, Mogensen, Fonden, Matto, & Mattila-Sandholm, 2000). To a lesser extent, *Enterococci*, *Streptococci, Propionibacterium, Lactococcus* and *Saccharomyces* spp. have also been used (Saarela et al., 2000). Previous studies have reported the positive effects of probiotics in systemic diseases, such as candida vaginitis (De Seta et al., 2014), dermatophytosis (Kumar, Mahajan, & Kamra, 2014), gastrointestinal infection (Hayama et al., 2014), and colon carcinoma (Wang, Zhang, & Shan, 2015; Zitvogel et al., 2015). Additionally, probiotics may assist the regulation of blood pressure (Khalesi, Sun, Buys, & Jayasinghe, 2014) and cholesterol levels (Jones, Tomaro-Duchesneau, Martoni, & Prakash, 2013). In dentistry, probiotics were first used for caries prevention, gingivitis, and periodontal conditions (Twetman, 2012). However, to date, the effect of probiotic agents on preventing oral candidiasis in the elderly population is conflicting (Hatakka et al., 2007; Ishikawa et al., 2015; Kraft-Bodi, Jorgensen, Keller, Kragelund, & Twetman, 2015). Probiotics may be effective in preventing candida-associated stomatitis in the elderly population according to Hatakka et al. and Kraft-Bodi et al., but adverse effects are also reported by Ishikawa et al. It is therefore essential to conduct a systematic review to summarize and critically appraise the available trials.

Hence, we here performed a *meta*-analysis and systematic review of the literature to assess the efficacy of probiotics in preventing candida-associated stomatitis in the elderly population.

2. Methods

2.1. Search strategy

This *meta*-analysis was conducted according to Reporting Items for Systematic Reviews and Meta-analyses recommendations (David Moher, Jennifer, Douglas, & the PRISMA Group, 2009), and was registered through the international prospective systematic review register system (registration number: CRD42016035863). A computer-based search of PubMed/Medline, EMBASE, and the Cochrane Library database was performed to obtain titles and abstracts of studies using the following search strategy: ((((((((((((Thrush[Title/Abstract]) OR Candidiases, Oral[Title/Abstract]) OR Oral Candidiases[Title/Abstract]) OR Oral Candidiasis[Title/Abstract]) OR Moniliasis, Oral[Title/Abstract]) OR Moniliases, Oral[Title/Abstract]) OR Oral Moniliases[Title/Abstract]) OR Oral Moniliasis[Title/Abstract])) OR "Candidiasis, Oral"[Mesh])) AND ((elderly[Title/Abstract]) OR "Aged"[Mesh])) AND ((probiotic[Title/Abstract]) OR "Probiotics"[Mesh])) AND ((randomized controlled trial[publication type] OR controlled clinical trial [publication type] OR randomized[title/abstract] OR placebo[title/abstract] OR randomly[title/abstract] OR trail[title/abstract] OR groups[title/abstract])) (PubMed), ('candidiasis'/exp OR 'candidas' OR 'monilia' OR 'monilias' OR 'torulopsis utilis' OR 'candida utilis') AND ('probiotic agent'/exp OR 'probiotic' OR 'probiotics') AND ('aged'/exp OR 'elderly')AND ('randomized controlled trial'/exp)(EMBASE), and ([candida] OR candidiasis: ti,ab,kw OR Candidiases: ti,ab,kw OR Thrush: ti,ab,kw OR Moniliasis: ti,ab,kw OR Moniliases: ti,ab,kw) AND ([probiotics] OR probiotics: ti,ab,kw) AND ([Aged]OR elderly: ti,ab,kw). (Cochrane Library). We also conducted manual searches of the reference lists of the identified papers as an adjunctive search. The search was limited to papers published in English from January 2004 to January 2017.

2.2. Study selection criteria

The inclusion criteria were as follows. (1) Randomized controlled trials that compared probiotics (at any dosage and in any form) with a placebo. (2) Subjects who were independent "healthy" elderly, aged 60–102 years, without restriction on patients' sex or race. (3) Studies with a substantive interventional aim of preventing oral candida infection by using probiotics, and reported on candidiasis that was assessed using the reference standard (i.e., by evaluating the viable counts of candida). (4) Studies that allowed the construction of at least one 2×2 table of test performance by extracting data from the study. (5) Studies that included more than 30 patients. Studies were excluded if the subjects included patients who infected with human immunodeficiency virus, had recently undergone organ transplants, or had heart disease.

2.3. Data extraction

Initially, two investigators independently selected and evaluated the abstracts that were found to meet the inclusion and exclusion criteria approximately. Once an investigator regarded the reference as eligible, the full-text article was obtained for a complete assessment. Secondly, two investigators independently evaluated the eligibility and quality of the full-text articles according to the inclusion and exclusion criteria. Another reviewer resolved discrepancies between these two reviewers based on the screening procedures. After excluding studies with serious design flaws, three articles encompassing four parameters were collected for the initial analysis (Fig. 1).

2.4. Risk of bias of the included studies

Two reviewers evaluated the risk of bias of the individual studies independently. The approach we used for assessing risk of bias in included studies was recommended by Cochrane reviews. According to Cochrane handbook a bias is a systematic error in results or inferences, which means that multiple replication of the same study would reach the wrong answer on average(Higgins, Deeks, Altman, & on behalf of the Cochrane Statistical Methods Group, 2011). The biases that were considered were as follows: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias) (Fig. 2).

2.5. Data synthesis and analysis

Review manager 5.2 (Cochrane IMS, Oxford, UK) was used to analyze reports and the odds ratios (ORs) were determined.

2.6. Statistical analysis

The data in each trial were extracted, and 2×2 tables (e.g., probiotics/comparison vs. high/low counts of candida) were constructed to calculate the relation between the viable counts of candida and the use of probiotics. We estimated the beneficial effect of using probiotics on oral candidiasis by means of OR and their respective 95% confidence intervals (CIs). Then, these estimates were combined using the Mantel–Haenszel method. Heterogeneity across trials was quantified with the I^2 metric. Since less than 10 studies were included, a funnel scatterplot was not used to estimate possible publication bias (Ioannidis, 2008).

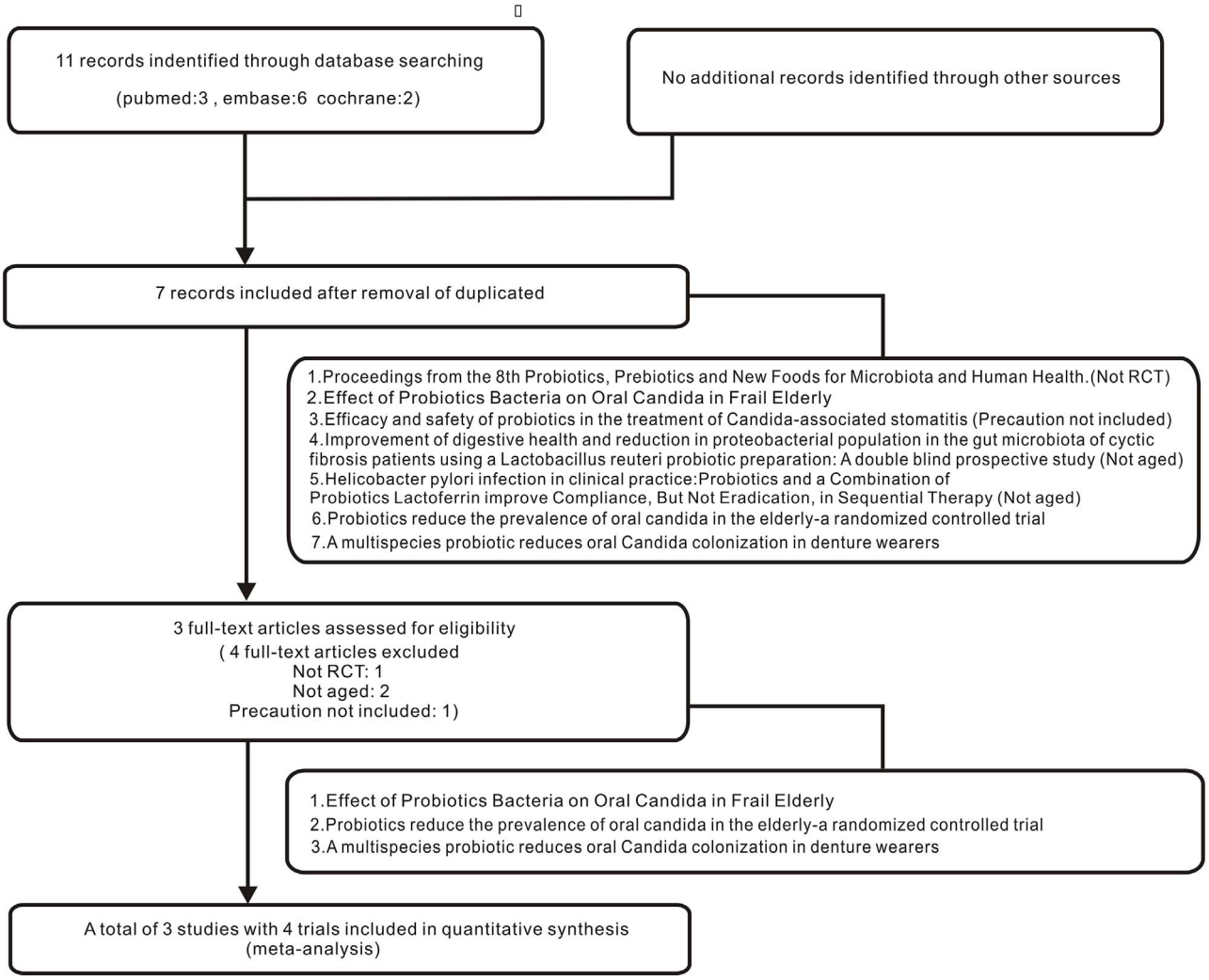

Fig. 1. Evidence search and exclusion process.

3. Results

3.1. Characteristics of included studies

Since Kraft-Bodi et al. (2015) measured candida counts in both saliva and plaque samples, we regarded this article as two studies. The total number of elderly in the included studies was 595. The baseline characteristics of the patients, the probiotics species, variations in the methods used, and therapy duration of the studies included in our systematic analysis are summarized in Table 1. The included studies allowed classification of candida levels according to counts, using colony-forming units (cfu) counted as $\geq 10^4$ cfu/ml as a cut-off to define this as a binomial (low/high) variable. The threshold for attrition rate in therapy duration was 32%.

3.2. Quality of included studies

The trials differed in regard to background, ethnicity, and education level of the study population. The definition of oral candidiasis and the probiotics used in the selected studies also differed. For uniformity, we defined oral candidiasis by a high candida count and included all species with documented use as probiotics. The risk of bias in the included studies was performed as shown in Fig. 2.

3.3. Effects of probiotics on preventing candidiasis

The total number of the participants was 595. The therapy duration ranged from 5 to 16 weeks in these trials. The studies containing the largest samples were those by Hatakka et al. (2007) and Kraft-Bodi et al. (2015), and subjects in these studies were followed up for 16 weeks and 12 weeks, respectively. The study with the smallest sample size was that by Ishikawa et al. (2015), and subjects were followed up for 5 weeks.

A test for heterogeneity yielded $\chi^2 = 2.69$ with three degrees of freedom, with $P = 0.44$, and with $I^2 = 0\%$, indicating high homogeneity (Higgins, Thompson, Deeks, & Altman, 2003). Since the included trials revealed clinically important effects with similar magnitude, the result of our *meta*-analyses was particularly clear (Higgins et al., 2003). No sub-group analyses for study quality were conducted for this reason. The ORs of the individual and pooled main outcomes are shown in Fig. 3. The four trials reported in the three articles yielded significant results, with an OR and CI lower than 1.0. The combined OR, as analyzed using the Mantel–Haenszel approach, was 0.54 (95% CI: 0.38–0.77) (Fig. 3). Thus, taken together, probiotic products were an effective means of decreasing the prevalence of high counts of oral yeasts measured as a binomial (high/low) variable.

In the trial by Hatakka et al. (2007), 192 eligible elderly individuals, from old-age homes and sheltered housing units, received 50 g of Emmental-type probiotic cheese (containing 15% fat) as a new precautionary measure; after adjusting for 13 independent risk factors for

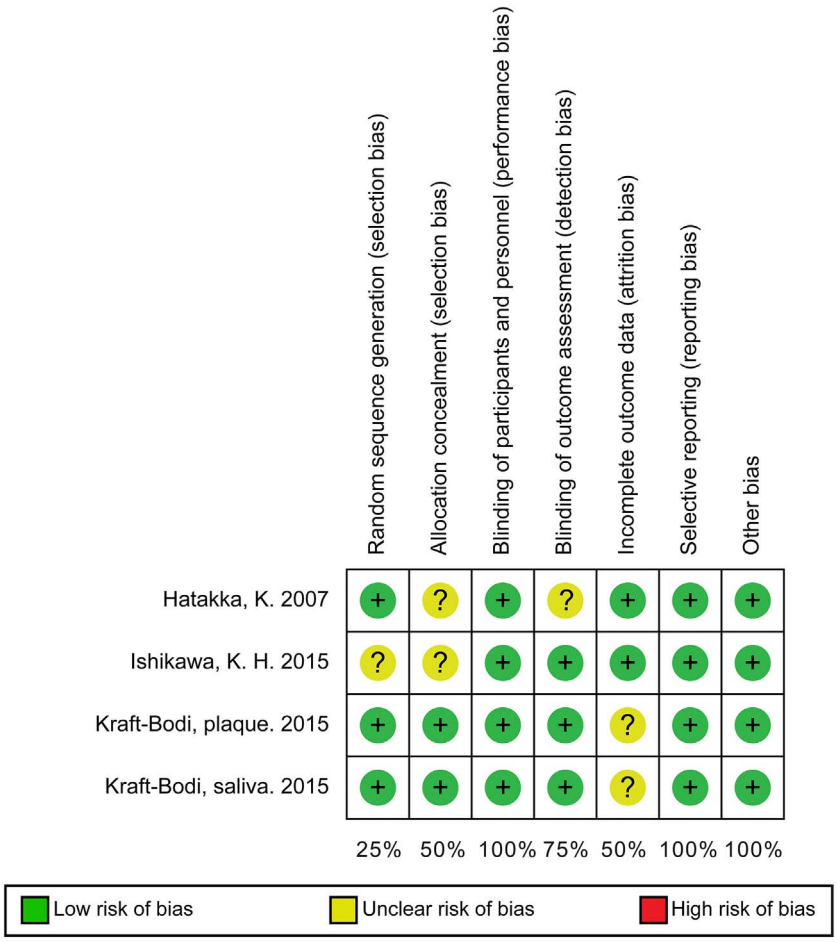

Fig. 2. Risk of bias summary. Review of authors' judgments about each risk of bias item for each included study and presented as percentages across all included studies.

candidiasis, probiotics were found to have a significantly preventative effect (OR: 0.51; 95% CI 0.26–0.97) (Hatakka et al., 2007).

In addition, Ishikawa et al. (2015) reported on a study that investigated the effect of probiotics as a precautionary measure against candidiasis in patients seeking dental treatment (complete dentures). *L. rhamnosus* HS111, *L. acidophilus* HS101, and *Bifidobacterium bifidum* were used in equal amounts; thus, subjects consumed a capsule containing 10^8 cfu (3.3×10^7 cfu of each) probiotics or placebo. Of the 55 volunteers enrolled, *C. albicans* was present in 52.1% of the patients at the beginning of the study. However, at the end of the follow-up, only three of 13 patients in the probiotic group still harbored *C. albicans*. Although there was no significant difference between the probiotics and placebo groups (OR: 1.24; 95% CI: 0.43–3.58), suggesting that probiotics were not protective against candida, the reduction in the incidence of oral candidiasis provided evidence to the contrary (Ishikawa et al., 2015).

The aim of the trial conducted by Kraft-Bodi et al. was to assess the effect of daily intake 2 lozenges containing a minimum of 10^8 cfu probiotic on the prevalence and counts of oral candida. He detected high candida counts in the saliva and plaque samples collected from patients (92% wearing maxilla dentures and 64% wearing mandibular dentures). At the end of treatment, high counts of candida in plaque samples were found in 24 of 82 individuals in the probiotic group, and 42 of 90 individuals in the placebo group. The corresponding values in saliva samples were similar, 19 of 84 individuals in the probiotic group and 33 of 90 individuals in the placebo group, respectively, indicating a positive preventative effect of probiotics (Kraft-Bodi et al., 2015).

In summary, probiotic agents were an effective factor in elderly patients, and decreased the prevalence of high counts of oral yeasts, as measured as a binomial (high/low) variable.

4. Discussion

The occurrence of oral candidiasis can be attributed in part to dysbiosis, an imbalance in the resident oral microflora. Probiotics are living microorganisms that can, when administered in adequate amounts, beneficially affect health (Sanders, 2008). Probiotic agents, which may defend against pathogenic microorganisms through competitive, antagonistic, and immunological effects, have been used to prevent candida-associated stomatitis by some clinicians. Multiple probiotic species have been used in clinical practice; these include *Lactobacillus* spp., *Bifidobacterium* spp. and many others (Cremonini

Table 1
Design of the included randomized, placebo-controlled trials.

References	Sample	Country of trial	No. of patients	Age range (years)	Probiotic species	Therapy duration
Hatakka et al. (2007)	Plaque	Finland	192	70–100	Lactococcus, Lactobacillus, Propionibacterium	16-week
Ishikawa et al. (2015)	Palatal	Brazil	55	Elderly individuals	*L. rhamnosus* HS111, *L. acidophilus* HS101, Bifidobacterium	5-week
Kraft-Bodi et al. (2015)	Plaque	Sweden	174	60–102	Lactobacillus	12-week
Kraft-Bodi et al. (2015)	Saliva	Sweden	174	60–102	Lactobacillus	12-week

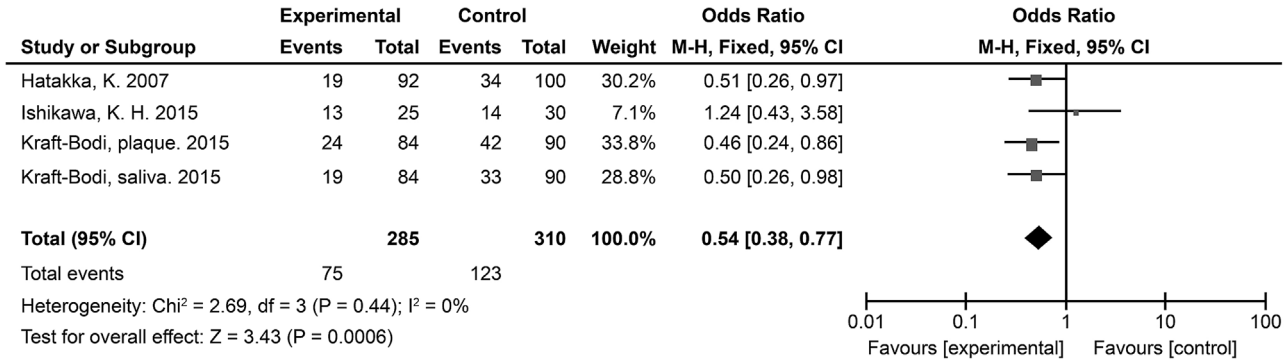

Fig. 3. Odds ratio and confidence intervals from individual studies. Forest diagrams showing crude and combined odds ratio for eligible studies. M-H, Mantel Haenszel. Probiotics vs placebo, outcome: high counts of candida (events).

et al., 2002). However, clinical data for the use of probiotic supplements for candidiasis are disappointingly few and conflicting. In this study, we included three articles reporting double-blind randomized placebo-controlled studies rather than a large number of uncontrolled studies, improving the validity of our analysis. We found that probiotic agents were an effective means for decreasing the prevalence of high counts of oral yeasts in elderly individuals.

Christian Jobin of the University of Florida College of Medicine in Gainesville stated “Different drugs, different bugs, but the same endpoint” (Leslie, 2015); however, the mechanisms by which different species exert their effects vary (Hasslof, Hedberg, Twetman, & Stecksen-Blicks, 2010a). Firstly, probiotics, as living microorganisms, can compete for binding sites, available substrates, and nutrients (Allaker & Douglas, 2009; Matsuzaki, Takagi, Ikemura, Matsuguchi, & Yokokura, 2007; Meurman, 2005; Sobel, 2007). In addition, based on a number of contemporary studies, it has been shown that probiotics (e.g., *Lactobacillus* species) hamper the growth of candida, based on antagonism in agar diffusion assays (Hasslof, Hedberg, Twetman, & Stecksen-Blicks, 2010b; Ujaoney et al., 2014). The same as bacteria (Chew, Cheah, Seow, Sandai, & Than, 2015). Additional studies have revealed mechanisms potentially involved in producing toxicant-like hydrogen peroxide (H_2O_2) (Strus et al., 2005; Verdenelli et al., 2014), acid, low-molecular-weight antimicrobial components, bacteriocins, and adhesins, which can all prevent the overgrowth of candida (Allaker & Douglas, 2009; Sobel, 2007). Furthermore, immunostimulation is a key means of fighting candida (Saarela et al., 2000). Such mechanisms can be explained by suppression of candida filamentation and mycelial development by active compounds, as evaluated using adhesion assays and observing hyphae formation (Ishijima et al., 2012; Murzyn, Krasowska, Stefanowicz, Dziadkowiec, & Lukaszewicz, 2010). Further studies are needed to test the functionality, safety, and efficacy in compromised patients prior to using them as therapeutic agents as well as for supplementation in health.

To determine whether probiotics are safe, we have searched electronic databases for pertinent articles from 2000 to 2017. Various forms of probiotic administration have been used in humans. None of the clinical trials have reported side effects that are directly related to probiotics, suggesting that they are safe.

The articles we have included in this review involved the use of different species, of which *Lactobacillus* and *Bifidobacterium* are most widely used in the current commercial market (Fuller, 1989). The primary experimental evidence suggests that the doses have been optimized; the amount of probiotics used in all studies only slightly exceeded the minimum level present in commercial products. Rybka and Kailaspathy assumed that probiotic yogurt should be consumed at a level of 10^6 cfu/ml as the minimum dose required to decrease the incidence of the disease (Rybka & Kailasapathy, 1995).

Given that different authors used different parameters to register and measure candidiasis, we used a classification of candidiasis based on counts, with a high count being a number of $\geq 10^4$ cfu/ml, irrespective of the clinical symptoms. However, raw data were used for four trials, which may lead to an incomplete evaluation. We showed overall prevention of oral candida by means of probiotic preparations in the trials included.

Publication bias is common in all clinical trials, and needs to be considered. Probiotics represent a new kind of functional food, raising concerns; there are no well-established or highly specific pharmacodynamics, to clarify the way to use probiotics in medicine, or that can describe their chemical and physical properties, or can define the mechanism of action (Matsubara, Mayer, & Samaranayake, 2016). There are also no studies showing side effects, which may not have been considered in clinical trials (Matsubara et al., 2016). The I^2 metric is the most popular measure for detection of heterogeneity in *meta*-analyses (Ioannidis, 2008). According to Cochran, I^2 ranges from 0% to 100%, and cut-offs are used to assess whether heterogeneity is present; 50% is taken as the cut-off for marked heterogeneity, 25% indicates little heterogeneity (Higgins et al., 2003; Ioannidis, 2008), and 0% indicates that there is no heterogeneity. Although we included only a few studies, we found that I^2 was 0%, indicating that the selected studies were adequate.

It is not clear whether our findings can be generalized to types of probiotic species other than those that were tested in the studies. Furthermore, the subjects that were enrolled in the clinical trials included in our *meta*-analysis were elderly patients, and hence, the results may be applicable to the elderly only. Moreover, although oral candidiasis results from local factors as well as systemic factors (Akpan & Morgan, 2002), an imbalance in the normal microflora remains the main pathogenic determinant (Coronado-Castellote & Jimenez-Soriano, 2013).

Although our *meta*-analysis suggests that probiotics play an active role in preventing oral candidiasis in elderly patients, further studies are necessary to confirm these findings in a larger-scale, world-wide, multicenter, prospective context. In addition, an exact standard for the preparation of probiotics has not been set. It is notable that the effect of probiotics, used as antimicrobials, is strain-specific and temporally specific in each patient; thus, it is necessary to select different probiotics as therapeutics for specific pathogens and to consider that their endpoint may not be the same (Hasslof et al., 2010a). Therefore, clinical trials performed on sufficient numbers of patients from different socioeconomic backgrounds are needed to develop a standard for probiotic formulation, dosage, administration schedules for oral candidiasis, reverse effects, and biodynamics in human beings. Furthermore, the cost-benefits should also be analyzed, to ensure easy access, low cost, and high efficiency.

Funding

This work was supported by grants from the Nonprofit Industry Research. Specific Fund of National Health and Family Planning Commission of China (No. 201502018), the National Natural Science Foundation of China (No. 81470747), the National Natural Science Foundation of China (No. 81321002), the International Science and Technology Cooperation Program of China (No. 2012DFA31370), the National Natural Science Foundation of China (No. 81200791, 81472533, 81102060, and 81270040). The funding agencies had no role in the study design, the collection, analysis, or interpretation of data, the writing of the report, or the decision to submit the article for publication.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgment

This review was supported by the Sichuan University.

References

Akpan, A., & Morgan, R. (2002). Oral candidiasis. *Postgraduate Medical Journal*, *78*(922), 455–459. http://dx.doi.org/10.1136/pmj.78.922.455.

Allaker, R. P., & Douglas, C. W. I. (2009). Novel anti-microbial therapies for dental plaque-related diseases. *International Journal of Antimicrobial Agents*, *33*(1), 8–13. http://dx.doi.org/10.1016/j.ijantimicag.2008.07.014.

Chew, S. Y., Cheah, Y. K., Seow, H. F., Sandai, D., & Than, L. T. (2015). Probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 exhibit strong antifungal effects against vulvovaginal candidiasis-causing Candida glabrata isolates. *Journal of Applied Microbiology*, *118*(5), 1180–1190. http://dx.doi.org/10.1111/jam.12772.

Coronado-Castellote, L., & Jimenez-Soriano, Y. (2013). Clinical and microbiological diagnosis of oral candidiasis. *Journal of Clinical and Experimental Dentistry*, *5*(5), e279–e286. http://dx.doi.org/10.4317/jced.51242.

Cremonini, F., Di Caro, S., Nista, E. C., Bartolozzi, F., Capelli, G., Gasbarrini, G., & Gasbarrini, A. (2002). Meta-analysis: The effect of probiotic administration on antibiotic-associated diarrhoea. *Alimentary Pharmacology & Therapeutics*, *16*(8), 1461–1467.

David Moher, A. L., Jennifer, T., Douglas Altman, G., & the PRISMA Group (2009). Reprint–preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Physical Therapy*, *89*(9), 873–880.

De Seta, F., Parazzini, F., De Leo, R., Banco, R., Maso, G. P., De Santo, D., ... Restaino, S. (2014). Lactobacillus plantarum P17630 for preventing Candida vaginitis recurrence: A retrospective comparative study. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *182*, 136–139. http://dx.doi.org/10.1016/j.ejogrb.2014.09.018.

Fisberg, M., & Machado, R. (2015). History of yogurt and current patterns of consumption. *Nutrition Reviews*, *73*(Suppl. 1), 4–7. http://dx.doi.org/10.1093/nutrit/nuv020.

Fuller, R. (1989). Probiotics in man and animals. *Journal of Applied Bacteriology*, *66*(5), 365–378.

Hasslof, P., Hedberg, M., Twetman, S., & Stecksen-Blicks, C. (2010a). Growth inhibition of oral mutans streptococci and candida by commercial probiotic lactobacilli – An in vitro study. *BMC Oral Health*, 10 Artn 1810.1186/1472-6831-10-18.

Hasslof, P., Hedberg, M., Twetman, S., & Stecksen-Blicks, C. (2010b). Growth inhibition of oral mutans streptococci and candida by commercial probiotic lactobacilli – An in vitro study. *BMC Oral Health*, *10*, 18. http://dx.doi.org/10.1186/1472-6831-10-18.

Hatakka, K., Ahola, A. J., Yli-Knuuttila, H., Richardson, M., Poussa, T., Meurman, J. H., & Korpela, R. (2007). Probiotics reduce the prevalence of oral candida in the elderly – A randomized controlled trial. *Journal of Dental Research*, *86*(2), 125–130.

Hayama, K., Ishijima, S., Ono, Y., Izumo, T., Ida, M., Shibata, H., & Abe, S. (2014). Protective activity of S-PT84, a heat-killed preparation of Lactobacillus pentosus, against oral and gastric candidiasis in an experimental murine model. *Medical Mycology Journal*, *55*(3), J123–129.

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ*, *327*(7414), 557–560. http://dx.doi.org/10.1136/bmj.327.7414.557.

Higgins, J. P. T., Deeks, J., Altman, D. G., & on behalf of the Cochrane Statistical Methods Group (2011). Chapter 8: Assessing risk of bias in included studies. In J. P. T. Higgins, & S. Green (Eds.), *Cochrane handbook for systematic reviews of interventions* Version 5.1.0 [updated March 2011.

Ioannidis, J. P. (2008). Interpretation of tests of heterogeneity and bias in meta-analysis. *Journal of Evaluation in Clinical Practice*, *14*(5), 951–957. http://dx.doi.org/10.1111/j. 1365–2753.2008.00986. x.

Ishijima, S. A., Hayama, K., Burton, J. P., Reid, G., Okada, M., Matsushita, Y., & Abe, S. (2012). Effect of Streptococcus salivarius K12 on the in vitro growth of Candida albicans and its protective effect in an oral candidiasis model. *Applied and Environmental Microbiology*, *78*(7), 2190–2199. http://dx.doi.org/10.1128/AEM.07055-11.

Ishikawa, K. H., Mayer, M. P., Miyazima, T. Y., Matsubara, V. H., Silva, E. G., Paula, C. R., ... Nakamae, A. E. (2015). A multispecies probiotic reduces oral Candida colonization in denture wearers. *Journal of Prosthodontics*, *24*(3), 194–199. http://dx.doi.org/10.1111/jopr.12198.

Jones, M. L., Tomaro-Duchesneau, C., Martoni, C. J., & Prakash, S. (2013). Cholesterol lowering with bile salt hydrolase-active probiotic bacteria, mechanism of action, clinical evidence, and future direction for heart health applications. *Expert Opinion on Biological Therapy*, *13*(5), 631–642. http://dx.doi.org/10.1517/14712598.2013.758706.

Khalesi, S., Sun, J., Buys, N., & Jayasinghe, R. (2014). Effect of probiotics on blood pressure: A systematic review and meta-analysis of randomized, controlled trials. *Hypertension*, *64*(4), 897–903. http://dx.doi.org/10.1161/HYPERTENSIONAHA.114.03469.

Kraft-Bodi, E., Jorgensen, M. R., Keller, M. K., Kragelund, C., & Twetman, S. (2015). Effect of probiotic bacteria on oral candida in frail elderly. *Journal of Dental Research*, *94*(Suppl. 9), 181s–186s. http://dx.doi.org/10.1177/0022034515595950.

Kumar, S., Mahajan, B. B., & Kamra, N. (2014). Future perspective of probiotics in dermatology: An old wine in new bottle. *Dermatology Online Journal*, *20*(9).

Lalla, R. V., Patton, L. L., & Dongari-Bagtzoglou, A. (2013). Oral candidiasis: Pathogenesis, clinical presentation, diagnosis and treatment strategies. *Journal of the California Dental Association*, *41*(4), 263–268.

Leslie, M. (2015). MICROBIOME. Microbes aid cancer drugs. *Science*, *350*(6261), 614–615. http://dx.doi.org/10.1126/science.350.6261.614.

Matsubara, V. H., Bandara, B. H., Mayer, M. P., & Samaranayake, L. P. (2016). Probiotics as antifungals in mucosal candidiasis. *Clinical Infectious Diseases*, *62*(9), 1143–1153.

Matsuzaki, T., Takagi, A., Ikemura, H., Matsuguchi, T., & Yokokura, T. (2007). Intestinal microflora: Probiotics and autoimmunity. *The Journal of Nutrition*, *137*(3 Suppl. 2), 798S–802S.

Meurman, J. H. (2005). Prbiotic: Do they have a role in oral medicine and dentistry? *European Journal of Oral Sciences*, *113*, 188–196.

Murzyn, A., Krasowska, A., Stefanowicz, P., Dziadkowiec, D., & Lukaszewicz, M. (2010). Capric acid secreted by S. boulardii inhibits C. albicans filamentous growth, adhesion and biofilm formation. *PLoS One*, *5*(8), e12050. http://dx.doi.org/10.1371/journal.pone.0012050.

Oliver, R. J., Dhaliwal, H. S., Theaker, E. D., & Pemberton, M. N. (2004). Patterns of antifungal prescribing in general dental practice. *British Dental Journal*, *196*(11), 701–703. http://dx.doi.org/10.1038/sj.bdj.4811354 discussion 687; quiz 707.

Patil, S., Rao, R. S., Majumdar, B., & Anil, S. (2015). Clinical appearance of oral Candida infection and therapeutic strategies. *Frontiers in Microbiology*, *6*(1391), http://dx.doi.org/10.3389/fmicb.2015.01391.

Pfaller, M. A. (2012). Antifungal drug resistance: Mechanisms, epidemiology, and consequences for treatment. *American Journal of Medicine*, *125*(Suppl. 1), S3–13. http://dx.doi.org/10.1016/j.amjmed.2011.11.001.

Rybka, S., & Kailasapathy, K. (1995). The survival of culture bacteria in fresh and freeze-Dried ab yogurts. *Australian Journal of Dairy Technology*, *50*(2), 51–57.

Saarela, M., Mogensen, G., Fonden, R., Matto, J., & Mattila-Sandholm, T. (2000). Probiotic bacteria: Safety, functional and technological properties. *Journal of Biotechnology*, *84*(3), 197–215.

Sanders, M. E. (2008). Probiotics: Definition, sources, selection, and uses. *Clinical Infectious Diseases*, *46*(Suppl. 2), S58–S61. http://dx.doi.org/10.1086/523341 discussion S144-151.

Sardi, J. C., Almeida, A. M., & Mendes Giannini, M. J. (2011). New antimicrobial therapies used against fungi present in subgingival sites-a brief review. *Archives of Oral Biology*, *56*(10), 951–959. http://dx.doi.org/10.1016/j.archoralbio.2011.03.007.

Sardi, J. C., Scorzoni, L., Bernardi, T., Fusco-Almeida, A. M., & Mendes Giannini, M. J. (2013). Candida species: Current epidemiology, pathogenicity, biofilm formation, natural antifungal products and new therapeutic options. *Journal of Medical Microbiology*, *62*(Pt 1), 10–24. http://dx.doi.org/10.1099/jmm.0.045054-0.

Sobel, J. D. (2007). Vulvovaginal candidosis. *The Lancet*, *369*(9577), 1961–1971.

Strus, M., Kucharska, A., Kukla, G., Brzychczy-Wloch, M., Maresz, K., & Heczko, P. B. (2005). The in vitro activity of vaginal Lactobacillus with probiotic properties against Candida. *Infectious Diseases in Obstetrics and Gynecology*, *13*(2), 69–75. http://dx.doi.org/10.1080/10647440400028136.

Twetman, S. (2012). Are we ready for caries prevention through bacteriotherapy? *Brazilian Oral Research*, *26*(Special issue 1), 64–70.

Ujaoney, S., Chandra, J., Faddoul, F., Chane, M., Wang, J., Taifour, L., ... Ghannoum, M. A. (2014). In vitro effect of over-the-counter probiotics on the ability of Candida albicans to form biofilm on denture strips. *Journal of Dental Hygiene*, *88*(3), 183–189.

Verdenelli, M. C., Coman, M. M., Cecchini, C., Silvi, S., Orpianesi, C., & Cresci, A. (2014). Evaluation of antipathogenic activity and adherence properties of human Lactobacillus strains for vaginal formulations. *Journal of Applied Microbiology*, *116*(5), 1297–1307. http://dx.doi.org/10.1111/jam.12459.

Wang, S., Zhang, L., & Shan, Y. (2015). Lactobacilli and colon carcinoma – A review. *Wei Sheng Wu Xue Bao*, *55*(6), 667–674.

Williams, D., & Lewis, M. (2011). Pathogenesis and treatment of oral candidosis. *Journal of Oral Microbiology*, 3. http://dx.doi.org/10.3402/jom.v3i0.5771.

Zitvogel, L., Galluzzi, L., Viaud, S., Vetizou, M., Daillere, R., Merad, M., & Kroemer, G. (2015). Cancer and the gut microbiota: An unexpected link. *Science Translational Medicine*, *7*(271), http://dx.doi.org/10.1126/scitranslmed.3010473 271ps271.