Journal of Taibah University Medical Sciences (2024) 19(2), 372–378

Taibah University

Journal of Taibah University Medical Sciences

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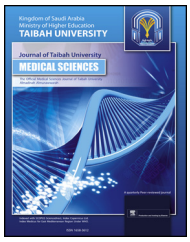

Review Article

Probing the antinociceptive and therapeutic potential of probiotics in managing temporomandibular joint arthritis

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Received 17 November 2023; revised 26 December 2023; accepted 23 January 2024; Available online 3 February 2024

الملخص

استكشفت مراجعة الأدبيات هذه التأثيرات المضادة للألم والعلاجية للعلاج بالبروبيوتيك في علاج حالات التهاب المفاصل التي تؤثر على المفصل الصدغي الفكي. تم البحث في قواعد البيانات المفهرسة دون قيود زمنية ولغوية حتى فبراير 2023 لتحديد الدراسات التي تناولت السؤال: "هل العلاج بالبروبيوتيك فعال في إدارة التهاب المفاصل الصدغي الفكي؟". تم استخدام الكلمات الرئيسية التالية كمجموعات مختلفة باستخدام العوامل المنطقية: التهاب المفاصل، والتهاب المفاصل العظمي، والألم، والبروبيوتيك، والروماتويد، واضطرابات الفك الفكي الصدغي، والمفصل الفكي الصدغي. كانت الدراسات السريرية والتجريبية الأصلية التي قيمت الفعالية العلاجية للعلاج بالبروبيوتيك لإدارة هشاشة العظام مؤهلة للإدراج. لم يتم طلب رسائل إلى المحرر والمراجعات والتعليقات ووجهات النظر وآراء الخبراء. تم تصميم هيكل المراجعة الحالية لتغليف المعلومات ذات الصلة. تم تحديد 297 دراسة ذات صلة خلال البحث الأولي في الأدبيات. أظهر التدقيق في النصوص الكاملة وقوائم المراجع لهذه الدراسات أنه حتى الآن لا يزال الدور المحتمل للعلاج بالبروبيوتيك في إدارة هشاشة العظام في منطقة المفصل الفكي الصدغي غير محقق. لا توجد تجارب سريرية في الأدبيات المفهرسة التي قامت بتقييم فعالية العلاج بالبروبيوتيك في إدارة التهاب المفاصل الصدغي الفكي. ومع ذلك، فإن هذا لا يمنع دورها المحتمل كعوامل مضادة للألم وعلاجية في المجموعات السكانية المعرضة للإصابة.

الكلمات المفتاحية: التهاب المفاصل؛ هشاشة العظام؛ ألم؛ بروبيوتيك؛ روماتيزمي؛ اضطرابات الفك الصدغي

Abstract

This literature review explored the antinociceptive and therapeutic effects of probiotic therapy (PT) in the treatment of arthritic conditions affecting the temporomandibular joint (TMJ). Indexed databases were searched without time and language restrictions up to and including February 2023, to identify studies addressing the question: "Is PT effective for the management of TMJ arthritis?" The following keywords were used in different combinations with Boolean operators: arthritis, osteoarthritis, pain, probiotic, rheumatoid, temporomandibular disorders, and temporomandibular joint. Original clinical and experimental studies assessing the therapeutic efficacy of PT in the management of osteoarthritis were eligible for inclusion. Letters to the editor, reviews, commentaries, perspectives, and expert opinions were not sought. The structure of the current review was tailored to encapsulate relevant information. A total of 297 relevant studies were identified during the initial literature search, and the full text and reference lists of these studies were scrutinized. To date, the potential role of PT in managing osteoarthritis of the TMJ region remains uninvestigated. No clinical trials in the indexed literature have assessed the efficacy of PT in managing TMJ arthritis; however, this finding does not preclude a potential role of probiotics as antinociceptive and therapeutic agents in susceptible populations.

Keywords: Arthritis; Osteoarthritis; Pain; Probiotic; Rheumatoid; Temporomandibular disorders

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Peer review under responsibility of Taibah University.

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 https://doi.org/10.1016/j.jtumed.2024.01.004

Introduction

The term arthritis is described as an intra-articular inflammatory condition and is commonly referred to as joint pain.[1] Arthritis is often associated with stiffness, pain, and disability of affected synovial joints, and osteoarthritis (OA) is the most common arthritis type.[2,3] Other forms of arthritis include rheumatoid arthritis (RA), psoriatic arthritis, gout, and fibromyalgia.[4,5] Between the years 1990 and 2020, the prevalence of arthritis increased from 15 % (affecting approximately 38 million individuals) to 18.2 % (affecting nearly 60 million individuals) in the United States.[6] The temporomandibular joint (TMJ) is a synovial joint with similar anatomy and function to those of the knee and hip joints. Temporomandibular disorder (TMD) is an umbrella term encompassing a variety of conditions that affect the TMJ, such as myofascial pain, internal joint derangement or jaw dislocation, ankylosis, and arthritis.[7,8] The incidence of TMJ arthritis is often underrated;[9,10] however, studies[11–13] have shown that OA is its most common form, and occurs in as much as 16 % of the population, more predominantly in females than males. Other arthritic conditions that affect the TMJ include RA, psoriatic arthropathy, and ankylosing spondylitis.[9] Risk factors commonly associated with the etiopathogenesis of arthritic conditions in the TMJ include trauma, parafunctional habits, and malocclusion.[7,14] The diagnosis of TMJ arthritis is facilitated by the integration of cone-beam computed-tomography and magnetic resonance imaging, along with consideration of clinical symptoms such as pain in the TMJ region, crepitus, and limited mouth opening.[14] Therapies often used in the management of TMJ arthritis include pharmaceutical medications, such as acetaminophen and non-steroidal anti-inflammatory drugs, occlusal splint therapy (OST), and surgery.[15,16]

Probiotics are live microorganisms (bacteria and yeasts) that offer health benefits when consumed or applied topically.[17–19] Changes in the gut and oral microbiota have been implicated in the development of various inflammatory diseases, including arthritis, because of the substantial influence of the gut–joint axis, which involves molecular pathways regulating the pathogenesis of such conditions.[20] Sophocleous et al.[21] have explored the influence of probiotic therapy (PT) (with *Lacticaseibacillus paracasei* [LP]) on the treatment of OA in 8-week old mice subjected to destabilization of the medical meniscus. The 6-week follow-up results indicated that PT inhibited cartilage damage at the medial femoral condyle and resulted in greater bone volume than observed in controls not receiving PT.[21] From a clinical perspective, Taye et al.[22] have assessed the effects of probiotic (*Lactobacillus rhamnosus* [LGG]) intervention on pain decrease in a 67-year-old Australian woman with OA of the right ankle and lower back. Compared with placebo admiration, LGG therapy resulted in a statistically significant decrease in OA-related self-rated pain scores measured via the visual analogue scale.[22] Similarly, Lei et al.[23] have evaluated the influence of probiotic *Lactobacillus casei* Shirota (LcS) on the management of knee OA in 537 patients. The results at 6 months' follow-up showed a significant decrease in self-rated knee pain (measured with the visual analogue scale) and serum C-reactive protein levels in the LcS group than the control group receiving placebo treatment. The authors have concluded that LcS therapy is an innovative treatment for the clinical management of knee OA.[23] These studies[21–23] have suggested that PT may potentially be effective in decreasing pain and improving healing in patients with OA of joints including the ankle, hip, lower back, and knee.

Given this background, the purpose of this literature review was to explore the potential therapeutic and antinociceptive effectiveness of PT in managing TMJ arthritis.

Materials and Methods

Ethical statement

This study involved a literature review of the relevant indexed literature. Consequently, obtaining prior approval for the study protocol from an institutional review board or ethics committee was unnecessary.

Focused question

Patients, Intervention, Control and Outcome (PICO) can be a useful tool for posing focused clinical questions. PICO helps clarify the question, and determine the search concepts and type of study that is most appropriate to answer the question type.[24] The addressed focused PICO question for the present study was: "Is PT useful for managing arthritis of the TMJ?"

PICO

Patients (P): Patients diagnosed with TMJ arthritis. Intervention (I): Administration of probiotics as a therapeutic approach for managing TMJ arthritis. Control (C): Placebo or conventional treatment (non-probiotic interventions). Outcome (O): Evaluation of the effectiveness of PT in alleviating TMJ arthritis symptoms and improving patients' overall condition.

Eligibility criteria

Clinical and experimental studies including case reports, case series, studies in animal models, randomized clinical trials, and case-control studies that addressed the focused question were considered eligible for inclusion.

Literature search

A literature search was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[25] Indexed databases (PubMed/Medline, Google Scholar, Scopus, and EMBASE) were searched by two authors (BML and FJ) without time and language restrictions. The literature search was performed up to and including February 2023, with different combinations of the keywords arthritis, osteoarthritis, pain, probiotic, rheumatoid, temporomandibular disorders, and temporomandibular joint, which were joined with Boolean operators (AND/OR). Full texts of potentially relevant original studies were independently read by two authors and judged with reference to the focused question and eligibility criteria. Disagreements regarding study eligibility were resolved via discussion with two additional authors (PER and DM). Reference lists of potentially relevant original and review articles were also hand-searched to identify studies that might have been missed during the initial electronic search.

Results

The initial search using the terms "arthritis" and "probiotic" yielded 303 studies. Filtering of the results with the terms "arthritis" OR "degenerative joint diseases" AND "temporomandibular joint" OR temporomandibular disorder" AND "probiotic" yielded zero studies (Figure 1).

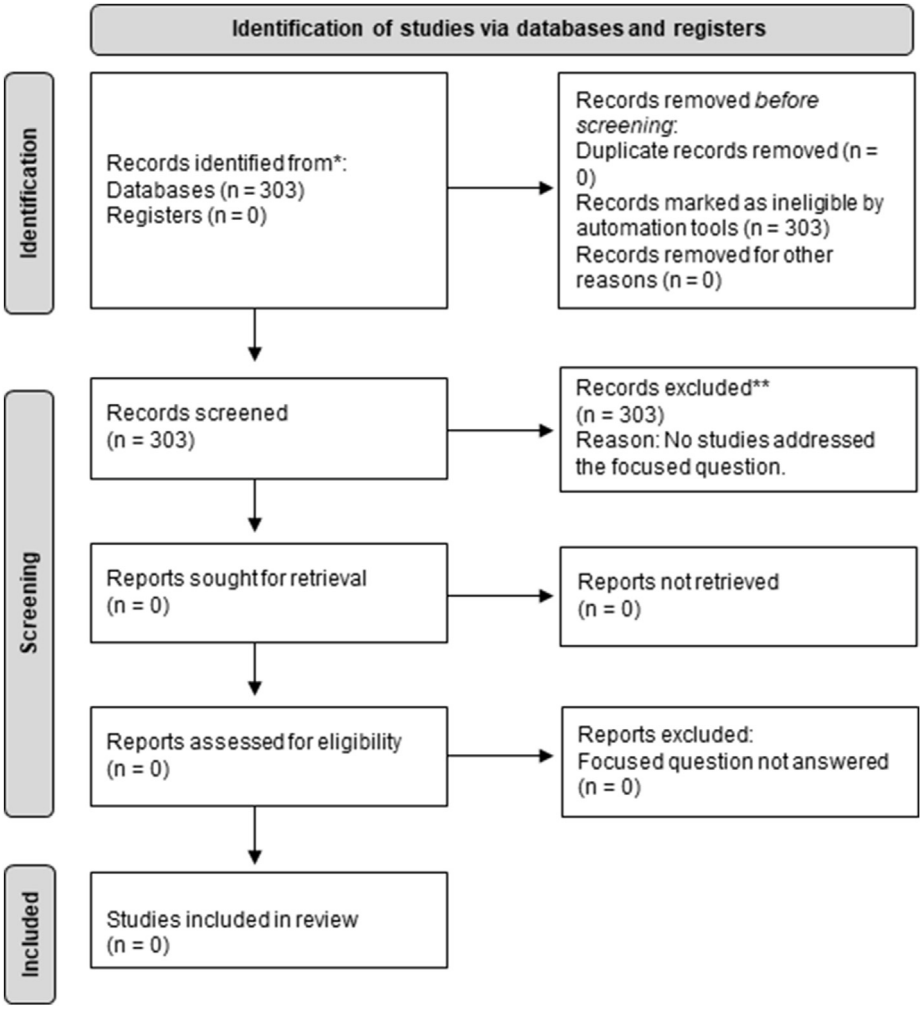

Figure 1: Literature search protocol.

Table 1: Overview of randomized controlled trials assessing the role of probiotic therapy in managing arthritis in systemic joints.

Authors	Patients (n)	Type of arthritis	Systemic joint	Study groups	Parameters assessed	Follow-up	Significant differences between test and control groups
Lei et al.[23]	537	OA	Knee	Test group: LcS Control group: placebo	Self-rated pain and serum CRP	6 months	Pain improved in the test group. Serum CRP was lower in the test group.
Vaghef-Mehrabany et al.[27]	46	RA	NR	Test group: LcS Control group: placebo	Self-rated pain, serum CRP, IL-6, IL-12, and TNFα	2 months	VAS improved in the test group. CRP, IL-6, IL-12, and TNFα were lower in the test group.
Alipour et al.[28]	46	RA	NR	Test group: LcS, LA, and BB Control group: placebo	Serum CRP, IL-10, IL-12, and TNFα	2 months	CRP, IL-10, IL-12, and TNFα were lower in the test group.
Zamani et al.[29]	60	RA	NR	Test group: LcS Control group: placebo	Serum cholesterol and CRP	2 months	Serum cholesterol and CRP were lower in the test group.

AS: ankylosing spondylitis; BB: *Bifidobacterium bifidum*; CRP: C-reactive protein; LcS: *Lactobacillus casei* Shirota; LA: *Lactobacillus acidophilus;* LR: *Lactobacillus rhamnosus* GR-1; IL: interleukin; NR: not reported; OA: osteoarthritis; RA: rheumatoid arthritis; TNFα: tumor necrosis factor alpha.

Table 2: Overview of experimental studies assessing the role of probiotic therapy in managing collagen-induced arthritis in rat-models.

Authors	Animals (n)	Age	Study groups	Euthanasia	Parameters assessed	Outcomes
Sophocleous et al.[21]	21 rats	8 weeks	Test group: LcP Control group: placebo	4 months	Histologic cartilage damage Bone health on micro-CT	Higher BV/TV in the test group Inhibited cartilage damage in the test group
Jhun et al.[34]	36 rats	6 weeks	Test group: LR Control group: placebo	~1 month	Pain behavior assessment[a] Protein expression in dorsal root ganglia	Decreased pain behavior and IL-1β expression in the test group
O-Sullivan et al.[36]	14 rats	11 weeks	Test group: LA Control group: placebo	2 months	Pain behavior assessment[b] Joint pathology	Decreased pain behavior in the test group Cartilage protection in the test group
Chang et al.[37]	14 rats	8 weeks	Test group: CB Control group: placebo	1.5 months	Pain behavior assessment[c]	Decreased pain behavior in the test group

BV/TV: trabecular bone volume; CB: *Clostridium butyricum*; CT: Computed tomography; Gln: glucosamine; IFNγ: interferon-gamma; LA: *Lactobacillus acidophilus*; LcP: *Lacticaseibacillus paracasei;* NR: not reported; LcS: *Lactobacillus casei* Shirota; LR: *Lactobacillus rhamnosus*.

[a] Performed with a dynamic plantar aesthesiometer.

[b] Assessed on Frey filament and hot plate testing.

[c] Static weight-bearing incapacitance test.

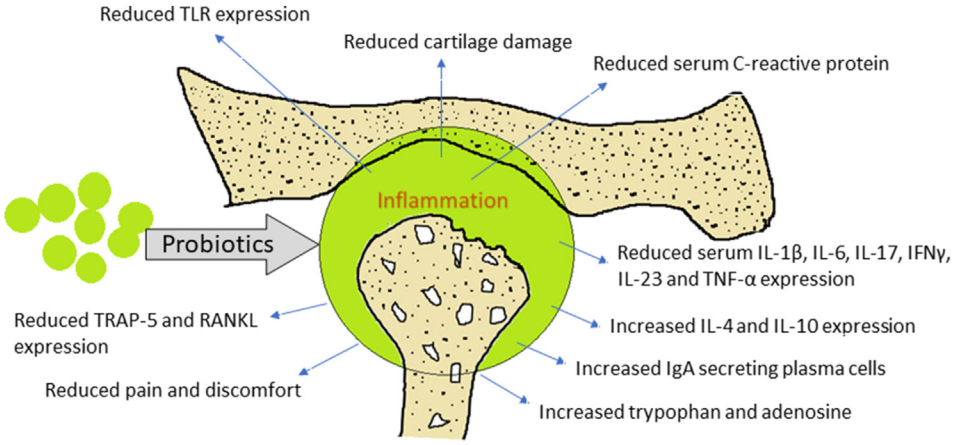

Figure 2: Hypothetical diagram of potential mechanisms through with probiotics might help manage arthritic conditions affecting the temporomandibular joint. IL: interleukin; IFNγ: interferon-gamma; RANKL: receptor activator of nuclear factor kappa-B ligand; TLR: Toll-like receptors; IgA: immunoglobulin A; TRAP-5: tartrate resistant acid phosphatase 5.

Discussion

After a careful review of the indexed databases, we observed a notable absence of any studies, including case reports and/or case series, exploring the potential effects of probiotics in the management of TMJ arthritis; however, this finding does not necessarily imply that probiotics are not potentially beneficial for this condition. We therefore proceeded to review the scientific literature (clinical and experimental studies) in which PT was used to treat arthritic conditions in systemic joints, such as the hip and knee joints. With regard to clinical evidence, we directed our attention toward randomized controlled trials (RCTs), because they are widely considered the gold standard for evaluating the efficacy of interventions and treatments.[26] An overview of the methods and outcomes of some RCTs[23,27–30] indicated that PT has positive effects on decreasing self-rated pain in systemic joints. The exact mechanisms through which PT may help decrease nociception in arthritis or other conditions are not yet fully understood, and further research is therefore required. However, a variety of potential mechanisms have been proposed in this regard. Probiotics enhance the production of neurotransmitters such as serotonin, which modulate pain and mood regulation.[31] Additionally, PT supplemented with *Lactobacillus reuteri* diminishes the expression of bone resorption markers, including receptor activator of nuclear factor kappa-B ligand, and tartrate resistant acid phosphatase 5, thereby inhibiting osteoclastogenesis.[32] In a systematic review of 15 studies, Kellesarian et al.[33] have evaluated the expression of destructive inflammatory cytokines (DICs) in the synovial fluid (SF) of patients with TMD (including arthritis). The expression of DICs such as TNFα, IL-6, IL-8, interferon-gamma, and IL-1β in the SF was higher among patients with rather than without TMD.[33] As shown in Table 1, probiotic administration decreased the expression of DICs in the serum in patients with systemic joint arthritic conditions such as OA, RA, and ankylosing spondylitis.[23,27–30] PT has been hypothesized to decrease the expression of DICs in the SF of systemic joints as well as TMJ. However, further studies are necessary in this context. To further understand the potential advantages of PT, we evaluated several studies[21,34–37] in animal models, which have examined the influence of PT on experimentally induced arthritis (Table 2). Intriguingly, the findings from these animal studies[21,34–37] aligned with those obtained from RCTs[23,27–30] regarding pain management and decreased expression of DICs in relation to arthritis. Moreover, in an experimental study,[35] PT has been found to increase the production of anti-inflammatory cytokines (IL-4 and IL-10), thus potentially decreasing pain sensation and inflammation in rats with experimentally induced arthritis. It is also worth mentioning that probiotics decrease nociception by modulating the activity of Toll-like receptors, thereby inhibiting excessive inflammation and thus decreasing pain levels. This mechanism suggests the potential of probiotics as a promising natural approach for pain management. On the basis of the available evidence, probiotics might potentially possess antinociceptive and anti-inflammatory properties, and therefore might be suitable agents for managing TMD, including TMJ arthritis. A hypothetical diagrammatic presentation of potential mechanisms through which probiotics may help manage arthritic conditions affecting the TMJ is shown in Figure 2.

On the basis of existing evidence from clinical and experimental studies, PT appears to have substantial promise as a potential treatment option for managing TMD. However, we must emphasize that PT should not be considered a substitute for conventional TMD treatments, such as OST. In a recent evidence-based review, Dadjoo et al.[7] have reported that adjuvant therapies such as acupuncture, exercise, botulinum toxin therapy, and photobiomodulation are effective therapeutic approaches for the management of TMD. Nevertheless, a consensus regarding the most potent adjuvant treatment for managing TMD continues to be debated. We note that in the experimental study by So et al.[35], use of PT as an adjunct to glucosamine (a natural compound found in cartilage) has been found to be more effective than PT alone in managing nociception and inflammation. Therefore, traditional OST in conjunction with PT might potentially be more effective than PT alone in managing

nociception and inflammation. Furthermore, lifestyle modifications such as routine yoga/exercise in conjunction with PT and OST/glucosamine therapies may be more effective in treating TMJ arthritis than treatment with probiotics alone. Further well-designed and power adjusted RCTs are needed to test these hypotheses. Determining which specific probiotic microbial strain would be most beneficial as an antinociceptive and anti-inflammatory agent for the management of TMJ arthritis remains a challenge. Moreover, the dosage and frequency of probiotic intake are likely to vary according to the severity of arthritis.

Although numerous questions regarding the role of PT in managing TMJ arthritis remain unanswered, the absence of definitive answers does not diminish the potential value of this treatment approach for addressing TMJ arthritis. The positive outcomes reported for other joints in the body (Table 1) suggest that PT might potentially have comparable effects on the TMJ. Further research and investigation are warranted to better understand PT effectiveness and application in this context.

Conclusion

No clinical trials in the indexed literature have assessed the efficacy of PT in managing TMJ arthritis; however, this finding does not preclude the potential role of probiotics as antinociceptive and therapeutic agents in susceptible populations.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical approval

Not required.

Authors contributions

FJ conceived and designed the study, supervised the research, and wrote and revised the manuscript. BML analyzed and interpreted data, prepared the tables, and wrote and revised the manuscript. DM performed the literature search, prepared the figures, and revised the manuscript before submission. PER performed the literature search, and wrote and revised the manuscript before submission. All authors have critically reviewed and approved the final draft, and are responsible for the content and similarity index of the manuscript.

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How to cite this article: Levenson BM, Rossouw PE, Michelogiannakis D, Javed F. Probing the antinociceptive and therapeutic potential of probiotics in managing temporomandibular joint arthritis. J Taibah Univ Med Sc 2024;19(2):372–378.