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Limosilactobacillus reuteri Improves Healing Following Fully Impacted Tooth Extractions: Randomized Clinical Trial

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ABSTRACT

Objectives: This randomized, double-blind, placebo-controlled clinical trial evaluated the effect of *L. reuteri* administration on postsurgical wound healing, pain levels, and patient-reported outcomes (PROs) following extraction of fully impacted teeth.

Methods: Consecutive patients requiring surgical extractions were included and randomly allocated to either test (probiotic) or control group (placebo). Following oral hygiene procedures, patients began a daily probiotic/placebo intake 7 days before surgery until 14 days after surgery. Follow-up was performed at 3 (T3), 7 (T7), and 14 (T14) days postop. Wound healing, postoperative complications, pain, perceived functional impairment, and Oral Health Impact Profile-14 (OHIP-14) were registered.

Results: A total of 128 patients (67 in the test group and 61 in the control group) were analyzed. Wound healing significantly improved in the test group at T3 and T7. Trismus was significantly milder in the test group at T3 and T14. No differences in pain were noted. The test group experienced reduced chewing impairment and difficulty in oral hygiene procedures, exhibited significantly lower scores of OHIP-14 at T14, and required a reduced number of anti-inflammatory medications in the first 7 days.

Conclusions: *Limosilactobacillus reuteri* administration improved wound healing, reduced the severity of trismus, and was associated with improved PROs following impacted tooth extractions.

Trial registration: The study protocol was registered in a clinical trials database (Clinicaltrials.gov) with registration number NCT04903925

1 | Introduction

The human microbiome is a complex system that contributes to the maintenance of good health status in humans (Ogunrinola et al. 2020). The human body is colonized by up to 500–1000 different bacterial species (Turnbaugh et al. 2007), with a higher genetic diversity than the human genome itself (Gilbert et al. 2018).

The oral cavity is one of the most colonized sites, hosting more than 600 bacterial species (Elavarasu et al. 2012) of which a good balance is required to maintain proper health and function ("Structure, function and diversity of the healthy Human Microbiome 2012").

Indeed, the host shares a symbiotic relationship with the human microbiome, which may be modulated by several factors, including antibiotics and probiotics (Ettinger et al. 2014). Antibiotics cannot selectively distinguish between pathogenic and non-pathogenic bacteria; therefore, their use may be associated with several side effects, such as bowel dysbiosis (Crobach et al. 2018).

The World Health Organization defines probiotics as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (Food and Agriculture Organization of the United Nations 2002). The use of probiotics is an emerging phenomenon in medicine, and the interest of the scientific community has strongly increased in recent decades. To date, there is evidence of the role of different probiotic strains in reducing symptoms of several medical conditions, such as bacterial vaginosis, antibiotic-associated diarrhea, and irritable bowel syndrome (Ettinger et al. 2014).

The mechanisms of action of probiotics are still not completely clear, and they may rely on competitive exclusion with pathogens (Dylag et al. 2014), the production of bacteriocins (Nes et al. 1996), and on epithelial cross-talk with the immune system (Walker 2008). In the field of dentistry, many studies support the use of probiotics to improve periodontal health status and halitosis (Invernici et al. 2018) and to prevent dental decay by reducing the number of cariogenic bacteria (Güngör et al. 2013).

Among all the possible applications of probiotics, their role in improving wound healing (Huseini et al. 2012) is one of the most interesting for oral surgery. Probiotics may contain several bacterial strains, and *Limosilactobacillus reuteri* (*L. reuteri*) showed effective antibacterial and anti-inflammatory properties (Vivekananda et al. 2010), making it promising to improve postsurgical wound healing. *L. reuteri* is a bacterium mainly detectable in saliva and crevicular fluid, capable of producing reuterin, which seems to play a role in preventing the overgrowth of pathogenic microorganisms (Jones and Versalovic 2009), and repressing inflammatory mediators such as tumor necrosis factor α (TNF-α), interleukin-8 (IL-8), and interleukin-1β (IL-1β) (Twetman et al. 2009).

So far, few studies have evaluated the applications of *L. reuteri* to improve postsurgical wound healing in clinical trials on punch biopsies (Twetman et al. 2018) and impacted third molar extractions and showed promising results (Ferrés-Amat et al. 2020; Wälivaara et al. 2019). However, a few studies about third molar extractions shared several limitations, including a small sample size, nonstandardized surgical procedures, and nonstandardized grade of impaction.

Tooth impaction is highly prevalent, and some authors suggest that this condition is present in 38% of the general population (da Silva Menezes et al. 2024). Most impacted teeth are third molars, followed by canines, premolars, and central incisors (Borges et al. 2014).

Often asymptomatic, impacted teeth may require extraction in case of pain, decay, periodontal disease, odontogenic pathology, infection, trauma, or for orthodontic reasons (Ghaeminia et al. 2020).

The grade of impaction may vary depending on the position of the tooth and the surrounding hard and soft tissue. Fully impacted teeth remain completely unerupted, enabling researchers to standardize postsurgical healing conditions to the greatest extent possible.

The primary aim of this randomized clinical trial was to evaluate the impact of *L. reuteri* administration on the postsurgical healing following the extraction of fully impacted teeth in a patient cohort.

The secondary aims were to evaluate postsurgical complications, the need for anti-inflammatory medications, patients' perception of the postsurgical recovery using the patient-reported outcome measures (PROMs), and the possible impact of *L. reuteri* in reducing gastrointestinal symptoms associated with antibiotic therapy. This paper is reported following the consolidated standards of reporting trials (CONSORT) statement (Cuschieri 2019).

2 | Materials and Methods

This randomized, double-blind, placebo-controlled clinical trial was conducted on patients requiring fully impacted tooth extractions at the University Hospital of Pisa (Italy) in the period between 2021 and 2023.

The study was approved by the local ethical committee (Northwestern Tuscany Ethics Committee, Approval Number: 18405), registered in a public registry of clinical trials (Clinicaltrials.gov Registration Number: NCT04903925), and followed the Declaration of Helsinki as amended in 2013 for studies conducted on human subjects (World Medical Association Declaration of Helsinki 2013).

All patients attending the University Hospital and fulfilling the inclusion criteria were considered potentially eligible for the study.

2.1 | Eligibility Criteria

2.1.1 | Inclusion Criteria

- Patients > 18 years of age.
- Patients requiring the extraction of a fully impacted tooth.
- Patients are able to understand and sign an informed consent form.

2.1.2 | Exclusion Criteria

- Patients < 18 years of age.
- Patients requiring the extraction of an erupted or partially impacted tooth.
- Patients with contraindications to oral surgery.
- Patients treated with immunosuppressive agents or immunocompromised.
- Patients treated with amino-bisphosphonate and anti-angiogenic medications.
- Patients treated with irradiation to the head and neck area.

- Patients with uncontrolled medical conditions.
- Patients in pregnancy or breastfeeding.
- Patients with drug and alcohol addiction.
- Patients with psychiatric disorders.
- Patients with allergy to penicillin or probiotics.

Teeth were classified as fully impacted if they had failed to erupt into their functional position in the oral cavity and were completely embedded in bone and/or soft tissue (Varghese 2021).

Upon enrollment, the patients underwent a full clinical and radiographic examination, and the need for a fully impacted tooth extraction was assessed. A Cone Beam Computed Tomography (CBCT) was requested in case of anatomical contiguity with vascular-neural structures visible on the Orthopantomogram (OPG). Moreover, complete medical history and drug intake were collected.

Patients were instructed on the purpose and timeline of the trial and asked to sign an informed consent to participate, and the tooth extraction was scheduled.

All patients included in the trial were randomly allocated to one of the two study groups with a computerized randomization list (simple random sampling without replacement). The randomization was performed by a researcher not involved in the evaluation of the patients at follow-up nor in the surgical procedures (R.I.), and the allocation was concealed.

Patients allocated to the test group were provided with the probiotic (GUM Periobalance, Sunstar, Switzerland) containing strains of *L. reuteri* ATCC PTA 5289 and DSM 17938 in lozenges formulation, to be dissolved in the mouth t.i.d. in the morning and evening, starting 7 days before surgery until 14 days after surgery (Krasse et al. 2006; Romani Vestman et al. 2015).

Patients allocated to the control group were provided with the placebo of the probiotic and instructed to follow the same dosage regimen.

The probiotic and placebo had identical packaging but lacked identifying labels, thus ensuring that patients were not aware of their group allocation (Figure 1).

Patient groups were designated as Group A and Group B. All investigators remained blinded to group assignments throughout the study, with blinding only broken for data interpretation and statistical analysis.

Prior to study initiation, all the investigators and operators involved in this study attended a 2-h calibration meeting to standardize clinical procedures and clinical evaluation protocols.

2.2 | Outcome Measures

2.2.1 | Surgical Procedures

On the day of the surgery (T0), clinical data were registered on a specific case report form (CRF) as follows:

FIGURE 1 | Probiotic and placebo packaging.

Tooth characteristics and position:

- Reason for tooth extraction: pericoronitis, cyst, decay, or orthodontic reasons.
- Intervention site: position of the tooth to be extracted. In the case of mandibular third molars, the grade of impaction and tooth angulation were evaluated according to Pell and Gregory (I, II, III and A, B, C) and Winter (vertical, mesio-angular, horizontal, disto-angular, bucco-lingual, and inverted) classifications.

Clinical parameters:

- Extraoral edema: assessed as clinically detectable swelling of the face. Measurements between the labial commissure and, respectively, the gonion (Go) and tragus (Tr) were performed with the aim of a measuring flexible tape and expressed in centimeters. An increase in either distance between T0 and follow-up was considered indicative of edema, which was expressed dichotomously (yes/no)
- Intraoral edema: assessed as visible swelling of the intraoral tissue and expressed dichotomously (yes/no)
- Suppuration: presence of pus discharge at the intervention site
- Local signs of inflammation: presence of redness, swelling, and pain
- Maximum mouth opening: evaluated with a caliper as the maximum length between upper and lower incisors

Patient-related parameters:

- Pain: assessed through the Numeric Rating Scale (NRS) ranging from 0 (absence of pain) to 10 (worst imaginable pain)
- Chewing impairment, speaking impairment, and difficulty in performing daily oral hygiene: all these parameters were evaluated according to the NRS (0–10)
- Oral Health Impact Profile 14 (OHIP-14) (Fernandes et al. 2006): 14-item tool to assess the Oral Health-Related

Quality of Life (OHRQoL) by addressing aspects of oral health affecting patients physical, psychological, and social well-being (Slade 1997). Each tool may be attributed with values from 1 (best) to 4 (worst), and the sum may vary between 14 and 56.

Moreover, patients were asked to report gastrointestinal symptoms in terms of dichotomic variables (presence/absence), such as gastric symptoms (pain or acidity), nausea, intestinal symptoms (pain, diarrhea, and constipation), and vomiting.

Tooth extractions were performed by two experienced oral surgeons with more than 10 years of experience in oral surgery (A.B. and F.G.) following a standardized surgical protocol (Figure 2).

A full-thickness envelope flap was raised, and the bone plate was exposed. In case of need, osteotomy and tooth sectioning were performed with surgical handpieces, and tooth removal was completed with elevators and forceps. Once the tooth was extracted, the alveolar cavity was carefully debrided and rinsed with saline to remove all debris. At the end of the procedure, the flap was repositioned with 4.0 resorbable sutures.

Tooth extraction characteristics, such as need for osteotomy and tooth sectioning and surgical times (starting from the incision to the end of suturing), were reported on the CRF.

After surgery, patients were provided with antibiotics to be taken after meals (amoxicillin b.i.d. for 6 days) and anti-inflammatory therapy (ibuprofen 600 mg, maximum t.i.d.) and were required to record their anti-inflammatory medication intake during the first 7 days following surgery.

Mouthrinses with 0.2% chlorhexidine were also prescribed b.i.d. for 7 days at least 120 min before taking probiotics, and patients were encouraged to continue the probiotic intake.

Patients were reevaluated 3 (T3), 7 (T7), and 14 (T14) days after surgery by two investigators not involved in the surgical procedures (C.C. and M.N.). Sutures were removed at T7.

2.2.2 | Follow-Up

During follow-up procedures, clinical, patient-related information, and gastrointestinal symptoms were recorded. In addition to the parameters evaluated at T0, the following parameters were assessed:

- Surgical site healing, evaluated through a wound healing score (Wachtel et al. 2003), attributing score 1 (excellent) in cases of complete closure of the wound in the absence of fibrin, score 2 (very good) to complete closure with a thin fibrin line, score 3 (good) to complete closure with a coagulum of fibrin, score 4 (bad) in the presence of wound dehiscence associated with partial necrosis, and score 5 (very bad) to wound dehiscence with extensive presence of necrotic tissue.
- Fever: body temperature higher than 37°C
- Bleeding on palpation: blood oozing on gentle palpation
- Presence of alveolar osteitis: pain associated with debris in the extraction socket
- Trismus: reduction of mouth opening as compared to T0, evaluated through the measurement of the maximum interincisal distance with a caliper at T0 and follow-up.
- Sensation of swelling: evaluated according to the NRS (0–10)
- Number of nights of disturbed sleep

2.3 | Sample Size Calculation

Sample size was calculated referring to one of the few studies evaluating the role of *L. reuteri* in wound healing following impacted tooth extractions (Wälivaara et al. 2019).

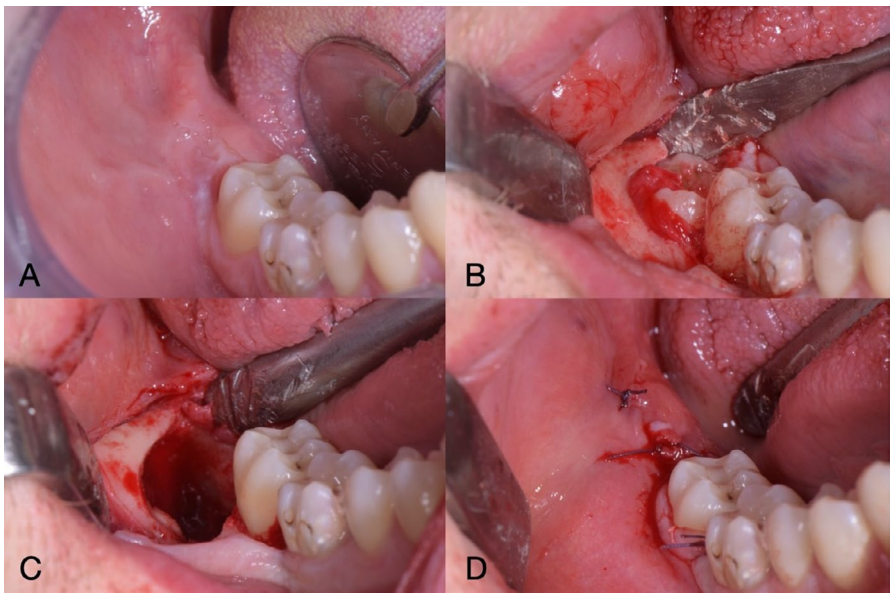

FIGURE 2 | Impacted tooth extraction: (A) presurgical clinical image, (B) flap elevation and tooth exposure, (C) postextraction socket, and (D) flap repositioning with sutures.

On this basis, with a level of significance of 5% and a power of 90%, 126 patients had to be recruited (63 per group).

Considering a possible dropout of 20%, 150 patients (75 per group) were enrolled.

2.4 | Statistical Methods

Statistical analysis was performed by a dentist expert in biostatistics (R.I.) who was neither involved in surgical procedures nor in data acquisition.

Descriptive statistics were reported as means, standard deviations, and medians.

The Shapiro–Wilk test was employed to verify the normal distribution of data. Depending on the distribution of the parameters, nonparametric tests were used. In case of quantitative or ordinal variables, comparison between groups was performed using the Mann–Whitney test. Dichotomous variables were analyzed using the chi-squared test or Fisher's exact test. Completion of at least 95% of the CRF was required for inclusion in the analysis. Missing data were managed by using imputation techniques. A per-protocol analysis was performed.

Statistical analyses were performed using XLStat software (XLSTAT 2023.1.4 (1408) statistical and data analysis solution, Addinsoft, Paris, France).

3 | Results

3.1 | Study Population

One hundred seventy patients were assessed for eligibility; 10 patients did not meet inclusion criteria (eight had partially impacted third molars, and two patients were allergic to amoxicillin), and 10 declined to participate in the study due to refusal to comply with study follow-up. One hundred fifty patients met the eligibility criteria and were randomized into the two experimental groups (75 patients per group). Of 75 patients in the test group, one patient decided against tooth extraction after the allocation, and seven patients did not attend one or more of the follow-up visits; therefore, eight patients were excluded from the analysis. In the control group, two patients did not undergo tooth extraction, and 12 were lost to follow-up. In total, 14 patients were excluded. The final sample included 128 patients (67 allocated to test group and 61 allocated to control group) who completed the study and whose data were analyzed.

The CONSORT flow diagram of the study is reported in Figure 3.

The sample was composed of 65 females and 63 men, with a mean age of 31.9 ± 11.9 years.

One hundred patients (78.12%) were nonsmokers, while 28 patients were light-smokers (4 ± 4.2 pack years). Regarding the medical history, 18 patients (14%) suffered from allergies (environmental or to medications), while 41 patients suffered from controlled systemic diseases (cardio-vascular diseases, hepatopathies or nephropathies, diabetes, gastritis, thyroid disorders, osteoporosis or anxiety disorders); finally, seven patients out of the total sample had co-morbidities (5.46%).

Demographic data and comparisons between groups are shown in Table 1.

No statistically significant differences were observed for demographic characteristics between groups.

3.2 | Surgical Intervention

Lower third molars represented 90.6% of the teeth extracted, followed by upper third molars (7.8%) and upper canines (1.6%).

In most cases, the reason for tooth extraction was pericoronitis (94.54%). Other reasons were the presence of follicular cyst (3.12%), tooth decay (1.56%), and orthodontics (0.78%).

All the tooth extractions were performed with a surgical flap approach, while osteotomy and tooth sectioning were performed in 123 (96.09%) and 107 (83.59%) of the cases, respectively. The mean surgical time was 31.98 ± 19.21 min in the test group and 29.28 ± 16.7 min in the control group, with no significant differences between groups ($p = 0.44$).

Tooth-related data and comparison between groups are shown in Table 2.

No statistically significant differences were observed for tooth-related variables between groups.

3.3 | Follow-Up Evaluation

The patients were reevaluated 3 (T3), 7 (T7), and 14 (T14) days after surgery.

The surgical wound healing index (WHI) at T3 was significantly improved in the test group (1.81 ± 0.85) compared to the control group (2.41 ± 1.09) ($p = 0.002$). The difference remained statistically significant 7 days following surgery ($p = 0.003$), whilst at T14 there were no significant differences between the two groups ($p = 0.076$).

More detailed information on the WHI in the two groups is shown in Table 3.

The clinical parameters evaluated at follow-up were the presence of extraoral and/or intraoral edema, suppuration, local signs of inflammation, trismus, fever, and alveolar osteitis (Table 4).

Among all the clinical parameters, statistically significant differences were observed for the presence of local signs of inflammation at T3, which were present in 26 patients of the test group and 39 patients of the control group ($p = 0.01$). Suppuration was detected at T7 in four patients of the control group ($p = 0.049$), and trismus at T14 occurred significantly more in patients of the control group ($p = 0.032$). Moreover, at T3 and T14, the test group

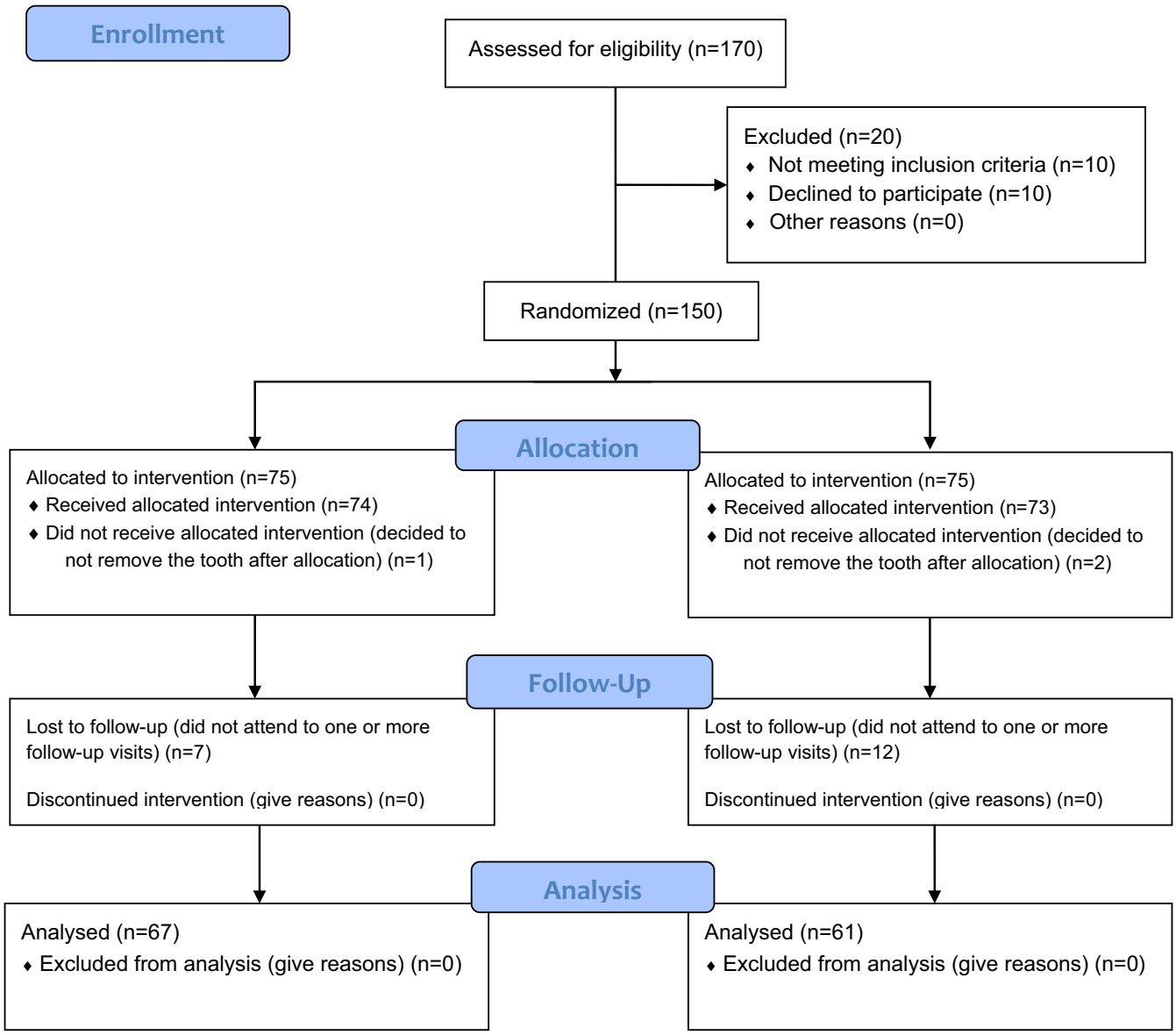

FIGURE 3 | CONSORT flow diagram of the study.

exhibited significantly lower severity of trismus, expressed as a decrease in maximum mouth opening compared with the control group (Table 5).

3.4 | Patient-Reported Outcomes

Pain, chewing impairment, speaking impairment, difficulty in performing daily oral hygiene, the OHRQoL assessed by the OHIP-14, sensation of swelling, and number of nights of disturbed sleep were registered for all patients at each time point (Table 6).

Patients of the test group experienced a reduced chewing impairment at T14 compared to the control group ($p = 0.014$), and a reduced difficulty in performing oral hygiene procedures ($p = 0.007$).

No statistically significant differences were found for the total number of nights of disturbed sleep ($p = 0.78$), which were on average 1.05 ± 1.74 for patients of the test group and 1.26 ± 2.14 for patients of the control group. OHIP-14 showed a statistically significant difference at T14, in favor of the test group ($p = 0.022$).

Gastrointestinal symptoms at every time-point and comparisons between groups are reported in Table 7; no statistically significant differences between groups were noted at any time-point.

Patients in the control group had a greater intake of anti-inflammatory medications (9.52 ± 5.57) in the first 7 days following surgery compared with patients in the test group (6.63 ± 4.85), with a statistically significant difference ($p = 0.001$).

4 | Discussion

The results of this RCT support the role of probiotics in improving postsurgical healing in the first 7 days following impacted tooth extractions. Overall, the results obtained appear reliable based on the post hoc power analysis of the Wound

TABLE 1 | Patients' demographic data and comparison between groups.

Patients $n = 128$	Test group (probiotic) $n = 67$	Control group (placebo) $n = 61$	p
Age			0.54
Mean ± SD	31.76 ± 12.34	32.15 ± 11.60	
Median	27	28	
CI	[28.81–34.72]	[29.24–35.06]	
Gender			0.86
Males (%)	32 (47.76%)	31 (50.82%)	
Females (%)	35 (52.24%)	30 (49.18%)	
Smoking habit (%)	13 (19.40%)	18 (29.51%)	0.26
Systemic health conditions			
Allergies	12 (17.91%)	6 (9.84%)	0.29
Cardiovascular diseases	5 (7.46%)	4 (6.56%)	0.88
Hepatopathies/nephropathies	1 (1.49%)	1 (1.64%)	1.00
Diabetes	1 (1.49%)	0 (0%)	1.00
Other diseases	17 (25.37%)	12 (19.67%)	0.57
Comorbidities	5 (7.46%)	2 (3.28%)	0.44

Healing Index (WHI)—which was set as primary outcome—and revealed a sufficient power (> 90%) and an adequate sample size.

The analysis of the WHI revealed significantly better outcomes in the test group compared to the control group during the first postoperative week. Additionally, patients receiving probiotics exhibited reduced signs of local inflammation 3 days after surgery, required fewer anti-inflammatory medications compared to patients treated with placebo, and experienced reduced trismus severity at three and 14 days after surgery.

The role of probiotics in promoting wound healing has been widely discussed in the literature. The health benefits of probiotics appear related to specific strains, due to the capacity of probiotics to modulate the production of cytokines and the activation of antimicrobial immune responses (Togo et al. 2021). For example, *Lactobacillus* strains can trigger both pro-inflammatory and anti-inflammatory cytokines, while *Bifidobacterium* strains are generally better at inducing anti-inflammatory responses (Kekkonen et al. 2008).

Oral probiotic intake may promote wound healing through several mechanisms. Firstly, it can influence the central nervous system by generating neuroactive compounds or altering the secretory functions of enteroendocrine cells in the gut lining, which leads to the release of neuromodulators that could enhance tissue repair. Secondly, probiotics can modulate the immune system by promoting lymphocyte recruitment to damaged tissues, thereby activating both innate and adaptive immune responses. Finally, they may enhance the absorption of vital nutrients—such as vitamins, minerals, and enzyme cofactors—that are crucial for skin tissue repair and wound healing (Lukic et al. 2017).

The transient efficacy of *L. reuteri* probiotics observed in this study—with significant improvements in wound healing at Days 3 and 7 but not at Day 14—suggests that probiotics exert their greatest therapeutic benefit during the early inflammatory and proliferative phases of socket healing (Twetman et al. 2009). This finding aligns with established probiotic mechanisms of action, including competitive exclusion of pathogens, immunomodulation (e.g., suppression of TNF-α and IL-6), and stimulation of collagen-producing fibroblasts, all of which are most active in the first week postextraction (Jeong et al. 2018; Twetman et al. 2009).

The lack of difference by Day 14 likely reflects the transition to host-dependent tissue remodeling, where systemic factors overshadow the localized microbial benefits of probiotics (Romani Vestman et al. 2015). These findings support a targeted probiotic regimen beginning 7 days preoperatively (to establish microbial and immunologic priming) and continuing for 7 days postoperatively (to cover the critical wound-healing window), while acknowledging that extended use may not provide additional benefits in uncomplicated cases.

However, in high-risk patients—such as those with diabetes, smokers, or immunocompromised individuals—extending probiotic use to 14 days postoperatively could be considered empirically, pending further research on strain-specific persistence and delayed-release delivery systems to prolong microbial colonization in extraction sockets.

Lactobacillus strains can be employed as an adjunct to the treatment of several dental, periodontal, and mucosal conditions (Gruner et al. 2016; Twetman and Jørgensen 2021). Moreover, the use of probiotics for the postoperative period following oral surgical procedures has been advocated to improve surgical outcomes.

TABLE 2 | Tooth-related data and comparison between groups. All data are expressed as *n* (%).

Teeth *n* = 128	Test group (probiotic) *n* = 67	Control group (placebo) *n* = 61	*p*
Tooth position			0.21
Lower third molars	58 (86.57%)	58 (95.08%)	
Upper third molars	7 (10.45%)	3 (4.92%)	
Canines	2 (2.98%)	0 (0%)	
Pell and Gregory classification[a]			0.097
I	6 (10.34%)	10 (17.24%)	
II	39 (67.24%)	27 (46.55%)	
III	13 (22.42%)	21 (36.21%)	
Pell and Gregory classification[a]			0.66
A	8 (13.79%)	8 (13.79%)	
B	28 (58.28%)	24 (41.38%)	
C	22 (37.93%)	26 (44.83%)	
Winter classification[a]			0.31
Vertical	12 (20.69%)	6 (10.34%)	
Mesio-angular	33 (56.90%)	42 (72.41%)	
Horizontal	10 (17.24%)	7 (12.08%)	
Disto-angular	3 (5.17%)	3 (5.17%)	
Bucco-lingual	0 (0%)	0 (0%)	
Inverted	0 (0%)	0 (0%)	
Reason for extraction			0.27
Pericoronitis	63 (94.03%)	58 (95.08%)	
Cyst	1 (1.49%)	3 (4.92%)	
Decay	2 (2.99%)	0 (0%)	
Orthodontics	1 (1.49%)	0 (0%)	
Surgical procedure			
Osteotomy	65 (97.01%)	59 (96.72%)	1.00
Tooth sectioning	53 (79.10%)	55 (90.16%)	0.085

[a]Percentages are calculated with respect to the number of lower third molars.

TABLE 3 | Wound healing index (WHI) at T3, T7, and T14 and comparison between groups. Data are expressed as means ± SD (median). Bold values: Statistically significant difference.

WHI	Test group (probiotic)	Control group (placebo)	p-value
T3			**0.002**
Mean ± SD	1.81 ± 0.85	2.41 ± 1.09	
Median	2	2.5	
CI	[1.61–2.01]	[2.14–2.68]	
T7			**0.003**
Mean ± SD	1.33 ± 0.67	1.87 ± 1.26	
Median	1	1	
CI	[1.17–1.49]	[1.55–2.19]	
T14			0.97
Mean ± SD	1.14 ± 0.55	1.15 ± 0.57	
Median	1	1	
CI	[1.01–1.27]	[1.01–1.29]	

Some authors (Banjonjit et al. 2022) evaluated the effects of *L. paracasei* on postoperative symptoms such as pain, swelling, and trismus in patients undergoing third molar removal and reported a significantly lower occurrence of trismus in the probiotic group. This is consistent with this study's findings and may suggest a relationship between the reduction of the severity of trismus and the use of probiotics. Moreover, we observed a reduced intensity of pain at T3 and T7 in the test group compared to the control group. Although this difference did not reach statistical significance, it may indicate a positive trend in favor of the probiotic group.

This study's findings showed that for mouth opening (maximum interincisal distance), there were statistically significant differences between probiotic and control groups on Days 3 and 14, but not Day 7, likely reflecting the complex interplay between probiotic-mediated anti-inflammatory effects and the natural progression of postoperative healing. The Day 3 improvement aligns with established evidence that *L. reuteri* suppresses early inflammatory mediators (IL-1β, TNF-α) that contribute to muscle trismus, as demonstrated by Vivekananda and colleagues (Vivekananda et al. 2010) in their study on postoperative inflammation. The loss of significant difference by Day 7 may represent a transitional phase where acute inflammation naturally subsides in both groups, while the reemergence of difference by Day 14 could reflect probiotic-enhanced tissue remodeling and reduced fibrosis, consistent with previous findings (Staab et al. 2009) regarding collagen organization. This biphasic pattern suggests probiotics may exert both early anti-inflammatory and later tissue-modulating effects, with a temporary convergence of outcomes during the proliferative phase (Day 7) when myofibroblast activity peaks regardless of intervention, as noted in several wound healing studies (Gurtner et al. 2008).

This pattern warrants further investigation into the temporal effects of probiotics on muscle fiber recovery and fascial healing, particularly comparing acute versus chronic inflammatory

TABLE 4 | Clinical outcomes and comparison between groups at T3, T7, and T14. All data are expressed as *n* (%). Bold values: Statistically significant difference.

	T3			T7			T14		
Clinical parameters	**Test group**	**Control group**	***p***	**Test group**	**Control group**	***p***	**Test group**	**Control group**	***p***
Extraoral edema	51 (76.12%)	49 (80.33%)	0.56	18 (26.87%)	18 (29.51%)	0.93	2 (2.99%)	6 (9.84%)	0.15
Intraoral edema	50 (74.63%)	46 (75.41%)	0.92	20 (29.85%)	14 (22.95%)	0.49	4 (5.97%)	3 (4.92%)	1.00
Suppuration	1 (1.49%)	3 (4.92%)	0.55	0 (0%)	4 (6.56%)	0.049	3 (4.48%)	0 (0%)	0.25
Local inflammation	26 (38.81%)	39 (63.93%)	**0.01**	12 (17.91%)	17 (27.87%)	0.29	2 (2.99%)	7 (11.48%)	0.08
Bleeding on palpation	15 (22.39%)	16 (26.23%)	0.76	2 (2.99%)	4 (6.56%)	0.42	2 (2.99%)	2 (3.28%)	1.00
Trismus	60 (89.56%)	54 (88.52%)	0.92	40 (59.70%)	40 (65.57%)	0.61	11 (16.42%)	21 (34.43%)	**0.032**
Fever ($T > 37°C$)	2 (2.99%)	1 (1.64%)	1.00	0 (0%)	1 (1.64%)	0.47	0 (0%)	0 (0%)	1.00
Alveolar osteitis	1 (1.49%)	3 (4.92%)	0.35	1 (1.49%)	4 (6.56%)	0.19	0 (0%)	1 (1.64%)	0.48

TABLE 5 | Maximum mouth opening at T0, T3, T7, and T14 and comparison between groups. Data are expressed in millimeters. Bold values: Statistically significant difference.

Maximum mouth opening	**Test group (probiotic)**	**Control group (placebo)**	***p***
T0			0.27
Mean ± SD	46.89 ± 7.87	45.07 ± 6.68	
Median	47	45	
CI	[45.01–48.77]	[43.39–46.75]	
T3			**0.034**
Mean ± SD	29.08 ± 6.99	26.47 ± 9.55	
Median	30	25	
CI	[27.41–30.75]	[24.07–28.87]	
T7			0.4
Mean ± SD	37.47 ± 8.65	35.59 ± 9.19	
Median	35	35	
CI	[35.40–39.54]	[33.28–37.90]	
T14			**0.002**
Mean ± SD	44.86 ± 7.41	40.41 ± 7.22	
Median	45	40	
CI	[43.09–46.63]	[38.50–42.22]	

markers in the masticatory muscles during the different postoperative phases. Day 7 convergence might also reflect measurement variability during the transition from acute edema resolution to tissue reorganization, suggesting future studies could benefit from more frequent assessments (e.g., daily measurements) during this critical period.

Additionally, the same authors (Banjonjit et al. 2022) observed lower TNF-α levels in the gingival crevicular fluid in the probiotic group, corresponding to reduced inflammation. Indeed, a reduction of the local signs of inflammation 3 days following surgery was observed in our sample, corroborating the hypothesis that probiotics may contribute to postoperative inflammation reduction.

Ferrés-Amat and colleagues (Ferrés-Amat et al. 2020) reported the absence of significant differences in infection rates while observing reduced pain and chewing difficulties in patients undergoing third molar extraction and receiving a combination of *Levilactobacillus brevis* CECT7480 (KABP-052) and *Lactoplantibacillus plantarum* CECT7481 (KABP-051), and a recent systematic review (Jørgensen et al. 2022) confirmed that, while probiotics may not affect the occurrence of postoperative infections, their administration might reduce the intensity of pain symptoms.

Some authors (Wälivaara et al. 2019) described the administration of *L. reuteri* following third molars extraction and found no significant differences in clinical wound healing or incidence of complications between the probiotic and control groups. However, patients receiving probiotics reported subjective benefits, such as reduced postoperative swelling and fewer nights of disturbed sleep, although no correlation with age or gender was observed. In our study, we employed *L. reuteri*-based probiotics as its strains have been isolated from the oral cavity (Twetman et al. 2017), and probiotic assumption was initiated 7 days prior to surgery. Wälivaara and colleagues (Wälivaara et al. 2019) started the probiotic administration just after surgery, potentially reducing the potential positive effects of probiotics on wound healing. Moreover, the authors reevaluated all the patients only at 14 days postoperatively, possibly underestimating the early effects of probiotic treatment on wound healing. The results of our trial are partially consistent with such findings, and they highlight the beneficial effects of probiotics on the early wound healing process with significantly better WHI, less trismus, and reduced anti-inflammatory medication intake in the

TABLE 6 | Patient-reported outcome measures and comparison between groups. Pain, chewing impairment, speaking impairment, difficulty in oral hygiene, and perceived Swelling are expressed as NRS 0–10. Bold values: Statistically significant difference.

	T3			T7			T14		
	Test group	Control group	*p*	Test group	Control group	*p*	Test group	Control group	*p*
Pain			0.068			0.072			0.25
Mean ± SD	2.82 ± 2.51	3.65 ± 2.60		1.57 ± 2.18	2.23 ± 2.46		0.29 ± 0.98	0.49 ± 1.16	
Median	3	3		0	1		0	0	
CI	[2.22–3.42]	[2.99–4.30]		[1.05–2.09]	[1.61–2.85]		[0.06–0.53]	[0.19–0.78]	
Chewing impairment			0.060			0.22			**0.014**
Mean ± SD	5.19 ± 3.15	6.21 ± 2.95		1.79 ± 2.50	2.46 ± 2.78		0.52 ± 1.41	1.55 ± 2.44	
Median	5	7		0.5	2		0	0	
CI	[4.44–5.94]	[5.47–6.95]		[1.19–2.39]	[1.76–3.16]		[0.18–0.86]	[0.94–2.16]	
Speaking impairment			0.15			0.96			0.28
Mean ± SD	2.34 ± 2.63	3.25 ± 3.20		0.45 ± 1.33	0.50 ± 1.34		0.30 ± 0.24	0.33 ± 0.18	
Median	2	2		0	0		0	0	
CI	[1.71–2.97]	[2.45–4.05]		[0.13–0.77]	[0.16–0.84]		[0.24–0.36]	[0.29–0.38]	
Difficulty in oral hygiene			0.31			0.15			0.007
Mean ± SD	3.92 ± 3.15	4.52 ± 2.92		1.47 ± 2.32	2.02 ± 2.58		0.33 ± 1.22	0.95 ± 1.77	
Median	5	5		0	0		0	0	
CI	[3.17–4.67]	[3.79–5.25]		[0.91–2.03]	[1.37–2.67]		[0.04–0.62]	[0.51–1.39]	
OHIP-14			0.40			0.11			**0.022**
Mean ± SD	21.44 ± 6.58	22.14 ± 6.29		17.24 ± 3.84	19.11 ± 6.66		14.78 ± 1.93	15.82 ± 3.05	
Median	20	22		16	17		14	14	
CI	[19.86–23.02]	[20.56–23.72]		[16.32–18.16]	[17.44–20.78]		[14.32–15.24]	[15.06–16.59]	
Perceived swelling			0.36			0.29			0.27
Mean ± SD	5.11 ± 2.55	5.54 ± 2.65		1.49 ± 2.15	1.69 ± 1.94		0.32 ± 1.10	0.58 ± 1.26	
Median	5	6		0	1		0	0	
CI	[4.499–5.721]	[4.875–6.205]		[0.975–2.005]	[1.20–2.18]		[0.057–0.58]	[0.26–0.90]	

TABLE 7 | Gastrointestinal symptoms and comparison between groups. Data are expressed as number of patients (%) experiencing the symptoms.

	T3			T7			T 14		
	Test group	Control group	*p*	Test group	Control group	*p*	Test group	Control group	*p*
Gastric symptoms	2 (2.99%)	4 (6.56%)	0.42	1 (1.49%)	1 (1.64%)	1.00	2 (2.99%)	0 (0%)	0.49
Intestinal symptoms	10 (14.93%)	7 (11.48%)	0.75	7 (10.48%)	10 (16.39%)	0.38	3 (4.48%)	1 (1.64%)	0.62
Nausea	3 (4.48%)	4 (6.56%)	0.71	1 (1.49%)	1 (1.64%)	1.00	2 (2.99%)	0 (0%)	0.49
Vomit	0 (0%)	2 (3.28%)	0.22	0 (0%)	0 (0%)	1.00	0 (0%)	0 (0%)	1.00

postoperative period. The significantly lower chewing impairment, difficulty in performing oral hygiene, and OHIP-14 scores detected in the test group at T14 further corroborate the effect of probiotic administration in reducing postoperative discomfort.

According to our results, improved wound healing in patients treated with probiotics represents a relevant finding. The benefits of probiotics in wound healing derive from the antagonist action towards pathogens through competition for nutrients and adhesion, while producing antimicrobial compounds such as lactic acid and bacteriocins (Kiousi et al. 2023). While for skin lesions, probiotic-based wound dressings may be employed (Bădăluță et al. 2024), in cases of oral surgical procedures, the oral dissolution of probiotics in the postoperative period can be the most effective administration route. The observed improvements in wound healing in patients treated with probiotics are consistent with previous reports (Wälivaara et al. 2019).

A reduced effect of probiotics regimen on gastrointestinal symptoms was observed, in contrast with other reports in the literature, which highlighted the benefits of probiotics on gastrointestinal functioning (Cinquini et al. 2021; Mullish et al. 2023; Yamada et al. 2024). These contrasting results may be attributed to the different bacterial strains employed in the studies, which may exert varying effects on the gut microbiota composition and function (Mullish et al. 2023).

However, in our sample, patients experienced only mild and self-limiting gastrointestinal symptoms, possibly because amoxicillin alone is less harmful for the gastrointestinal microbiota than when taken in association with clavulanic acid (Cinquini et al. 2021; Iglesias-Martin et al. 2014). Additionally, ibuprofen—prescribed as anti-inflammatory therapy in the present study—is the NSAID that is relatively less harmful for the stomach (Langman et al. 1994). However, the limited sample size and the relatively low incidence of gastrointestinal symptoms may have reduced the ability to detect statistically significant differences between groups. Future studies with larger cohorts focusing specifically on gastrointestinal symptoms should be conducted.

This study has several strengths, including an adequate sample size, a standardized surgical procedure, an early and continuous evaluation of wound healing (T3, T7, and T14), and a randomized double-blind design.

On the other hand, it also has several limitations. First, the concomitant use of chlorhexidine and antibiotics could have partially impaired the effects of probiotics on wound healing. However, *L. reuteri* DSM 17938 proved to be resistant to penicillin (Neut et al. 2017) and the probiotic assumption was postponed 2 h after the use of antibiotics and chlorhexidine to further reduce the possible interaction (Boyanova and Mitov 2012). Additionally, the wound healing index employed for the evaluation of fully impacted tooth extraction sites was originally conceived for periodontal assessment (Wachtel et al. 2003). This may represent a limitation while highlighting the unmet need for a dedicated wound healing classification for fully impacted tooth extractions. Moreover, the short follow-up period (14 days) may have limited the observation of different healing patterns over time. Finally, placebo effects were not controlled through blinding procedures, and patient adherence to postoperative care protocols was not objectively monitored.

Nevertheless, this study establishes a foundational protocol for the systematic administration of probiotics in the perioperative management of impacted tooth extractions, demonstrating clinically meaningful improvements in postoperative outcomes.

While these findings require validation in larger cohorts, they represent the first methodical approach to probiotic timing, duration, and strain selection specifically tailored to dentoalveolar surgery—addressing a significant gap in current perioperative care protocols. The results particularly highlight probiotics' role in mitigating trismus and early-stage healing complications, offering a safe adjunct to conventional postoperative care.

5 | Conclusion

Probiotics are a valuable adjunct to peri-operative treatment regimens following fully impacted tooth extractions. The present data support a reduction of local signs of inflammation, a reduction of trismus, and an improvement of surgical wound healing in patients receiving probiotics compared to placebo, suggesting a potential beneficial effect in modulating postoperative symptoms while improving wound healing.

Author Contributions

Chiara Cinquini: writing – original draft, investigation, conceptualization, methodology. **Rossana Izzetti:** writing – original draft, validation, visualization, data curation, formal analysis. **Marco Nisi:** investigation, writing – review and editing, data curation. **Francesco Gulia:** investigation, visualization, writing – review and editing. **Berta Garcia Mira:** methodology, validation, writing – review and editing. **Antonio Barone:** conceptualization, methodology, supervision, project administration, resources.

Ethics Statement

The study was approved by the institutional IRB (Northwestern Tuscany Ethics Committee) with approval number 18405 of the 3rd December 2020.

Consent

Written informed consent was obtained from all patients to participate in the present study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Research data are not shared.

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