Dear Editor;

The emergence and continuous spread of antimicrobial-resistant organisms (AROs) has raised global concerns for health authorities. According to CDC reports, there are annually more than 2.8 million antibiotic-resistant infection cases as well as 35,000 deaths in the United States [1]. AROs infection has led to an increased risk of fatal outcomes e.g. hospitalization length stays, mortality rate, as well as high treatment cost. Current pieces of evidence suggested that drug-resistant gram-negative bacteria can be spread among the community by fecal-oral route throughout intestinal colonization in humans [2]. In addition, intestinal carriage of multidrug-resistant bacteria is linked to subsequent severe infections such as sepsis, and abdominal, disseminated as well as urinary tract infections for their hosts [3]. The human gut microbiota plays an important role in the host’s health via decolonization or hindering the overgrowth of potentially pathogenic bacteria. Thus, intestinal colonization with AROs could be facilitated the further transmission of incurable infections to other individuals [4,5]. According to previous pieces of literature, systemic antibiotic treatment does not effective in the gut eradication of multi-drug resistant Enterobacteriaceae [6]. Oral antibiotics also have limited long-term effects on this issue [7]. Moreover, excessive antibiotic usage has been associated with dangerous outcomes particularly disrupting the normal gut microbiome as well as the development of antibiotic-resistant strains [8].

Recently, probiotics have been introduced as the solution to this problem. Probiotics are a group of live microorganisms with health-promoting attributes that are commercially available in different brands and mixtures. Based on existing assumptions, probiotics hinder the AROs intestinal carriage using various routes including 1) production of acids and toxins, 2) competitive adherence, 3) encouragement of a robust immune response, and 4) strengthening intestinal barriers, particularly a thickness mucosa production [9]. Probiotics have been proved to reduce intestinal colonization of drug-resistant bacteria in animal models [10,11]. However, there are conflicting results on the efficacy of probiotics regarding intestinal decolonization of multidrug-resistant organisms (MDRO) in the present human randomized clinical trials (RCTs) [12]. To be honest, it remains largely unknown specifically how the microbiota may facilitate or prevent this event. To determine the true effects of probiotics in the restoration of gut normal flora after the acquisition of MDROs, we performed a comprehensive statistical analysis on the present human trials. There are fourteen clinical studies regarding the efficacy of probiotics in the resolution of MDRO in individuals who have intestinal carriage (Table 1).

We evaluated the effectiveness of probiotics in both cures of multidrug-resistant organisms from the human intestinal tract as well as prevention of acquisition of new AROs in the population that received probiotics using the 1,287 data. The findings suggested that probiotics have not been significantly superior to placebo in the eradication of intestinal carriage with MDROs (OR: 2.45; 95%CI: 0.68–8.78; p-value: 0.16). Furthermore, there is no advantage regarding the efficacy of probiotics in the prevention of intestinal colonization with AROs (OR: 1.24; 95%CI: 0.88–1.75; p-value: 0.21).

Generally, statistical analysis of the current available RCTs revealed that probiotics are not meaningfully superior to placebo treatment in the reduction of intestinal antimicrobial-resistant organism colonization. Previously, the ESCMID/EUCIC guidelines in 2019 declared that current evidence is insufficient to provide recommendations for the efficacy of probiotics in the decline of intestinal colonization rate caused by aminoglycoside-resistant Enterobacteriaceae (AGRE), colistin-resistant Gram-negative organisms (CoRGN), carbapenem-resistant Acinetobacter baumannii (CRAB), cotrimoxazole-resistant Stenotrophomonas maltophilia (CRSM), fluoroquinolone-resistant Enterobacteriaceae (FQRE), pan-drug-resistant Gram-negative organisms (PDRGNB) and extremely drug-resistant Pseudomonas aeruginosa (XDRPA) [27]. We believed that the true role as means of eradicating intestinal carriage of MDRO currently remains uncertain. Therefore, further high-quality studies are needed to evaluate this with proper detail. Irrefutably, high bacterial diversity is generally advantageous, but a few bacterial species have health benefits. In addition, the efficacy of probiotics in specific strains. Probiotics are safe for immunocompetent individuals, but making changes in the gut microbial community may be harmful, particularly in immunocompromised individuals who may be at risk of gut microbiota disruption due to other factors [28]. Recently, McFarland et al., 2019 has been suggested the efficacy of Saccharomyces boulardii CNCM I-745 supplementation in a significant reduction of travelers’ diarrhea [8]. However, several factors may have affected overall estimates of the efficacy of probiotics in the eradication of intestinal carriage with AROs at present. First, there is a difference in probiotics supplementation course that the shorter course of probiotic supplementation may have contributed to the negative results. Second, the prevalence of comorbidities was various in relevant studies, infection rate was evidently higher among immunocompromised individuals. Third, probiotic formulations that were administered in these studies were several and affected overall estimates. We evaluated the efficacy of LGG® in the reduction of intestinal colonization with MDRO that was not significant (OR: 1.42; 95%CI: 0.69–2.89; p-value: 0.3). Fourth, the sample size may not have been large enough to detect a difference. Fifth, patients were receiving concurrent probiotics plus antibiotics, antibiotics likely had activity against administered probiotics, thus, intervals between antibiotics administration with probiotic supplementation should be taken into account. Lastly, it is hard to estimate the margin of clinical significance in the available studies that affected estimates. There are many uncertainties about the efficacy of probiotics in the
eradication therapies for MDROs. Current pieces of evidence have not been sufficiently assessed for their potential efficacy. Remaining elusively is the optimal administration route, the definition of dosage, and frequency of administration. As previously stated, the unexpectedly low success rate of probiotics may be due to the limitation of these studies. Thus, in order to determine whether probiotics play a significant role in eradicating intestinal carriage with MDRO, future studies should be adequately powered with standard design on the efficacy of probiotics supplementation in the reduction of intestinal carriage with antimicrobial-resistant organisms.

**Ethical approval**

There is no need for ethical approval.

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None.

**Author contribution**

Mohsen Karbalaei: Writing and Editing the draft. Masoud Keikha: Study design, data collection, Writing and Editing the draft. All authors read and approved the final version of the manuscript.

**Consent**

Not applicable for this study.

**Table 1**

| First author | Year | Country | Probiotics treatment | follow-up | Diagnostic method | Infection type | Population size | Cure/Colonization | Comparison probiotics | Ref |
|--------------|------|---------|----------------------|-----------|------------------|----------------|-----------------|-------------------|----------------------|-----|
| Sullivan     | 2004 | Sweden  | Lactobacillus        | twice daily for 14 days | 1 month 8 weeks | Fecal culture | ESBL            | 20                | 1/10                 | [13] |
| Manley       | 2007 | Australia| LGG®                | twice daily for 4 weeks | 1 month 8 weeks | Fecal culture | VRE             | 23                | 8/11                 | [14] |
| Regt         | 2010 | Netherlands| Ecologic AAD®         | twice daily for 4 months | twice daily for 5 weeks | Fecal culture | ARE             | 436               | 28/110               | [15] |
| Tannock      | 2011 | New Zealand| Mutaflor®            | twice daily for 5 weeks | 5 weeks | Fecal culture | MDR Escherichia coli | 69                | 11/36                 | [16] |
| Consuegra    | 2014 | Spain   | Simbiotic Drink®     | twice daily | ND | Stool or rectal-swab culture | MDRO | 89                | 12/46               | [17] |
| Doron        | 2015 | USA     | LGG®                | twice daily for 14 days | ND | Fecal culture | rectal swabs culture | Cure rate 11/18 | [18] |
| Nouvenne     | 2015 | Italy   | ND                  | twice daily for 14 days | ND | Stool or rectal-swab culture | CPKP | 133               | 10/18               | [19] |
| Kwon         | 2015 | USA     | LGG®                | twice daily for 14 days | once daily for one week | Fecal culture | MDRO | 70                | 6/30                 | [20] |
| Salomao      | 2016 | Switzerland| Lactobacillus         | twice daily for 14 days | twice a day for one week | Rectal swabs culture | MDR-GNB | 101               | 8/48                 | [21] |
| Eggers       | 2018 | USA     | L. rhamnous          | twice daily for 4 weeks | 4 weeks | Stool or rectal-swab culture | MRSA | 63                | 5/34                 | [22] |
| Dall         | 2018 | Denmark | Dicoflor®           | twice daily for 14 days | ND | Fecal culture | rectal swabs culture | Cure rate 6/26 | [23] |
| Ljungquist   | 2020 | Sweden  | Vivomixx®           | twice daily for 2 weeks | 1-year | ESBL, CPE | 80                | 5/40                 | [24] |
| Wieers       | 2021 | Belgium | Bactiol duo®        | twice daily for 14 days | 2-year | Fecal culture | Stool or rectal-swab文化 | Cure rate 54 | [25] |
| Rauzeo       | 2021 | USA     | LGG®                | twice daily for 14 days | ND | Fecal culture | rectal swabs culture | Cure rate 88 | [26] |

VRE: vancomycin-resistant enterococcus; ARO: antimicrobial-resistant organisms; MDR-GNB: multidrug resistant gram-negative bacilli; ESBL: extended spectrum beta-lactamase; MDRO: multidrug resistant organism; ARE: Ampicillin-resistant Enterococcus faecium; MDR-GNB: multidrug-resistant Gram-negative bacilli.

**Registration of research studies**

1. Name of the registry: Not applicable.
2. Unique Identifying number or registration ID: Not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): Not applicable.

**Guarantor**

All the authors of this paper accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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**Declaration of competing interest**

None.

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