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ORIGINAL CONTRIBUTION

The effect of probiotics on inflammatory biomarkers: a meta-analysis of randomized clinical trials

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Abstract

Purpose No study has summarized earlier findings on the effect of probiotic supplementation on inflammatory biomarkers. This systematic review and meta-analysis was conducted to systematically review the available placebo-controlled clinical trials about the effect of probiotic supplementation on several inflammatory biomarkers in adults.

Methods Relevant papers published up to March 2018 were searched up through PubMed, MEDLINE, SCOPUS, EMBASE, and Google Scholar, using following suitable keywords. Clinical trials that examined the effect of probiotic supplementation on inflammation in adults were included.

Results Overall, 42 randomized clinical trials (1138 participants in intervention and 1120 participants in control groups) were included. Combining findings from included studies, we found a significant reduction in serum hs-CRP [standardized mean difference (SMD) −0.46; 95% CI −0.73, −0.19], TNF-a (−0.21; −0.34, −0.08), IL-6 (−0.37; −0.51, −0.24), IL-12 (−0.47; −0.67, −0.27), and IL-4 concentrations (−0.48; −0.76, −0.20) after probiotic supplementation. Pooling effect sizes from 11 studies with 12 effect sizes, a significant increase in IL-10 concentrations was seen (0.21; 0.04, 0.38). We failed to find a significant effect of probiotic supplementation on serum IL-1B (−0.17; −0.37, 0.02), IL-8 (−0.01; −0.30, 0.28), and IFN-g (−0.08; −0.31, 0.15) and IL-17 concentrations (0.06; −0.34, 0.46).

Conclusions Probiotic supplementation significantly reduced serum concentrations of pro-inflammatory cytokines including, hs-CRP, TNF-a, IL-6, IL-12, and IL-4, but it did not influence IL-1B, IL-8, IFN-g, and IL-17 concentrations. A significant increase in serum concentrations of IL-10, as a anti-inflammatory cytokine was also documented after probiotic supplementation.

Keywords Diet · Probiotic · Inflammation · Cytokine · Meta-analysis

Abbreviations

SMD	Standardized mean difference
T2DM	Type 2 diabetes mellitus
MtS	Metabolic syndrome

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CVD	Cardiovascular disease
NAFLD	Non-alcoholic fatty liver disease
SCFAs	Short-chain fatty acids
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
CRP	C-reactive protein
TNF-a	Tumor necrosis factor-a
SD	Standard deviation
SE	Standard error
MD	Mean difference
RCT	Randomized clinical trial
GALT	Gut-associated lymphoid tissue
IL	Interleukin
IL-1B	Interleukin 1 beta
IFN-g	Interferon-gama

Introduction

Inflammation is a part of innate immunity response to protect the body against injury and harm [1, 2]. However, chronic low-grade systematic inflammation is associated with higher risk of several chronic diseases including type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome (MtS), cardiovascular disease (CVD) [3, 4], and non-alcoholic fatty liver disease (NAFLD) [5].

Adoption of a physically active life-style may attenuate low-grade inflammation [6, 7]. In addition, diet can also play a role in this condition [8]. For instance, higher consumption of processed and fried foods has been linked to increased risk of inflammation [9]. In contrast, adherence to a dietary pattern rich in fibers might decrease inflammatory cytokines which may be due to incremented production of short-chain fatty acids (SCFAs) in the colon [10]. SCFAs are physiologically active byproducts of fermentation by microflora which are suggested to modulate systemic inflammation [11].

Probiotics are non-pathogenic microorganisms which when administered in adequate amounts confer several health benefits in improving conditions associated with inflammation [12]. Probiotic supplementation will change intestinal microbium to increase production of SCFAs [13]. Probiotic supplementation has attenuated inflammation-related diseases such as cardiovascular disease, allergies, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), autoimmune diseases, and cancers [14, 15]. Studies on the effect of probiotics supplementation on inflammatory cytokines are conflicting. Although some studies have found significant reduction in inflammatory cytokines after supplementation with probiotics compared to placebo [16, 17], some others could not reach the same effect [18, 19]. A recent systematic review and meta-analysis of clinical trials indicated that prebiotics significantly reduce serum C-reactive protein (CRP), where symbiotic reduced CRP and tumor necrosis factor-a (TNF-a), as compared to placebo [10].

Despite several publications on the effect of probiotics on different inflammatory biomarkers, no further study has summarized the findings from the previous studies in this regard. Therefore, we aimed to systematically review the available placebo-controlled clinical trials about the effect of supplementation with probiotics on several inflammatory biomarkers in adults and to do a meta-analysis, if possible.

Methods

Search strategy

Relevant studies published up to March 2018 were searched through PubMed, MEDLINE, SCOPUS, EMBASE, and Google Scholar, using the following suitable MESH and non-MESH keywords: ("Lactobacillus"[All Fields] OR "Streptococcus"[All Fields] OR "Saccharomyces"[All Fields] OR "Enterococcus"[All Fields] OR "Bifidobacterium"[All Fields] OR "Probiotic"[All Fields] OR "Lactococcus"[All Fields]) AND ("Inflammation"[All Fields] OR "inflammatory biomarker"[All Fields] OR "Tumor necrosis factor"[All Fields] OR "C-Reactive protein"[All Fields] OR "Transforming growth factor beta"[All Fields] OR "Cytokine"[All Fields] OR "Acute phase reactant"[All Fields] OR "Matrix metalloproteinase"[All Fields] OR "Intercellular adhesion molecule-1"[All Fields] OR "Monocyte chemotactic protein 1"[All Fields] OR "Inflammation Mediator"[All Fields] OR "Adipokine"[All Fields] OR "Interleukin"[All Fields] OR "Systemic inflammation"[All Fields]) AND ("Clinical Trial" OR "trial"). No restrictions of language or time of publication were used. To avoid missing any publication, we also examined reference lists of all included studies as well as review articles. Unpublished data and grey literatures, including dissertations, congress abstracts, and patents, were not included in the current meta-analysis. In addition, we removed duplicate citations.

Inclusion criteria

All randomized clinical trials that investigated the effect of probiotic supplementation on inflammatory biomarkers in adults were included. In case of several publications with the same data set, we included only the most complete one. If data for specific subgroups were reported, results for the whole population were used for the meta-analysis, unless it was not available. Moreover, when a study was performed on separate groups of participants, data of each group in

comparison with the control group were considered as an independent study.

Exclusion criteria

Studies that: (1) were conducted on animal models, pregnant or lactating women, and studies with children or only elderly participants; (2) did not have random allocation; (3) had an observational design; (4) examined the effect of another intervention along with probiotic supplementation; (5) examined postprandial inflammatory responses after an immediate intervention; (6) had no control group; (7) used symbiotic as the intervention; (8) used probiotic enriched foods; (9) examined only gene expression of inflammatory biomarkers; and (10) examined concentrations of inflammatory biomarkers in specific cell lines, were excluded.

Data extraction

The following data were extracted by two independent reviewers: first author's name, publication year, subjects' heath condition, study sample size, participants' sex, number of subjects in each groups, participants' age, type of probiotic microbes, trial design (parallel/cross-over), type of control, duration of intervention, mean and standard deviation (SD) concentrations of inflammatory biomarkers after intervention in each groups, mean (SD) changes in inflammatory biomarkers after intervention in each groups, and covariates. If data were reported as standard errors (SEs) or interquartile ranges, they were converted to SDs using appropriate formulas. When concentration of an inflammatory biomarker was reported in different units, it was converted to the most frequently used one.

Statistical analysis

The overall effect sizes were calculated as mean differences (MDs) and SEs of concentrations of inflammatory biomarkers between probiotic and control groups. If mean (SDs) changes were not reported, we took end-of-trial means (SDs) of biomarkers in each group. Then, we used fixed-effects model to calculate overall effect size, because random-effects model gives larger weights to small extreme studies [20]. Between-study heterogeneity was examined by the Cochran's Q test and I^2 statistic. To find probable sources of between-study heterogeneity, we conducted subgroup analyses based on participants' health condition (healthy/gastrointestinal disease/skeletal disorders/metabolic diseases/allergy and autoimmune diseases/renal diseases/critically ill/other diseases), sex (male/female/both genders), age (adult/adult + elderly), study design (parallel/cross-over), supplement dosage (< 1/1–10/10–100/≥100 CFU/day), duration of intervention (< 10 weeks/≥ 10 weeks), outcome assessment method (immunoassay/electrochemiluminescence/bead assay), and probiotic type (lactobacillus/bifidobacter/saccharomyces/different types), using a fixed-effects model. All statistical analyses were done using Stata software, version 11.2 (Stata Corp, College Station, TX, USA). $P < 0.05$ was considered as statistically significant.

Results

Study characteristics

Overall, 42 publications with 46 effect sizes were included in this meta-analysis [16–19, 21–58]. The flow diagram of study selection is shown in (Supplementary Figure 1). All studies were randomized clinical trials (RCTs), published between 2003 and 2018. Duration of intervention was varied from 1 to 52 weeks. A total of 1138 participants in intervention group and 1120 participants in control group were enrolled in these studies (43.22% male and 56.78% female). Characteristics of included studies are summarized in (Supplementary Table 1).

Among publications included, 40 studies were parallel RCTs [16–19, 21–29, 31–41, 43–58], whereas two remaining studies had cross-over design [30, 42]. These 46 effect sizes were related to studies in healthy subjects [31, 37, 39, 45, 46, 51], patients with gastrointestinal diseases [17, 19, 25, 32, 33, 44, 47, 49], patients with skeletal disorders [18, 22, 32, 34–36, 53, 58], those with metabolic diseases [23, 24, 29, 40, 50], those with allergy and autoimmune diseases [32, 38, 41, 43, 56, 57], patients with renal disease [26, 42, 48, 52, 55], critically ill patients [16, 28], and the remaining among patients with HIV [54], heart failure [27], edetulous [30], and depression [21]. Two effect sizes were from studies were done in men [23, 43], seven effect sizes from studies on women [22, 31, 32, 35, 41, 50, 53], and 37 effect sizes from studies on both genders [16–19, 24–34, 36–40, 42, 44–49, 51, 52, 54–58].

Probiotics administered were lactobacillus in 12 studies [18, 19, 22, 23, 30, 34, 37, 41, 46, 51, 53, 57], bifidobacter in 4 studies [32, 39, 44, 56], and saccharomyces in two studies [27, 54], whereas 24 studies used more than 1 type of probiotic [16, 17, 21, 24–26, 28, 29, 31, 33, 35, 36, 38, 40, 42, 43, 45, 47–50, 52, 55, 58]. Daily dose of probiotic bacteria was ranged from 0.06 to 1800 billion. Moreover, three studies did not report daily dose of consumed bacteria [17, 27, 57]. Placebo was used in all studies. Four studies had a third arm intervention [16, 25, 33, 45], which was not entered in the current meta-analysis. Adjustment for the baseline measures of inflammatory biomarkers was conducted in 14 studies [21, 22, 25, 31, 37–40, 44, 45, 50, 52, 53, 58], while 4 studies did not report any adjustment [16, 23, 33, 42].

Biochemical analyses were conducted using immunoassay [17–19, 21–26, 29, 33, 35, 37, 38, 40, 41, 44, 45, 47, 49–58], electrochemiluminescence [32], and bead assay [30, 31, 46]. In addition, nine studies did not report methods used to quantify inflammatory biomarkers [16, 27, 28, 34, 36, 39, 42, 43, 48].

Findings on the effect of probiotics on hs-CRP

Combining findings from 31 studies with 33 effect sizes, we found a significant reduction in serum hs-CRP concentrations after probiotic supplementation, as compared to placebo [standardized mean difference (SMD) −0.39; 95% CI (−0.50, −0.28), $I^2 = 83.8\%$] (Fig. 1). However, a significant between-study heterogeneity was found. Subgroup analysis by the participants' age and sex, study duration and outcome assessment method did not provide any explanation for between-study heterogeneity (Table 1). When the subgroup analysis was done based on health status of participants, between-study heterogeneity was disappeared. In this analysis, the effect of probiotic supplementation on hs-CRP was significant in participants with all health conditions except for patients with metabolic diseases and those with allergy and autoimmune diseases. In addition, subgroup analysis based on the type and dose of supplemented bacteria resulted in the disappearance of between-study heterogeneity for studies used lactobacillus and bifidobacter and those used ≥ 100 CFU/day of bacteria, respectively. In addition,

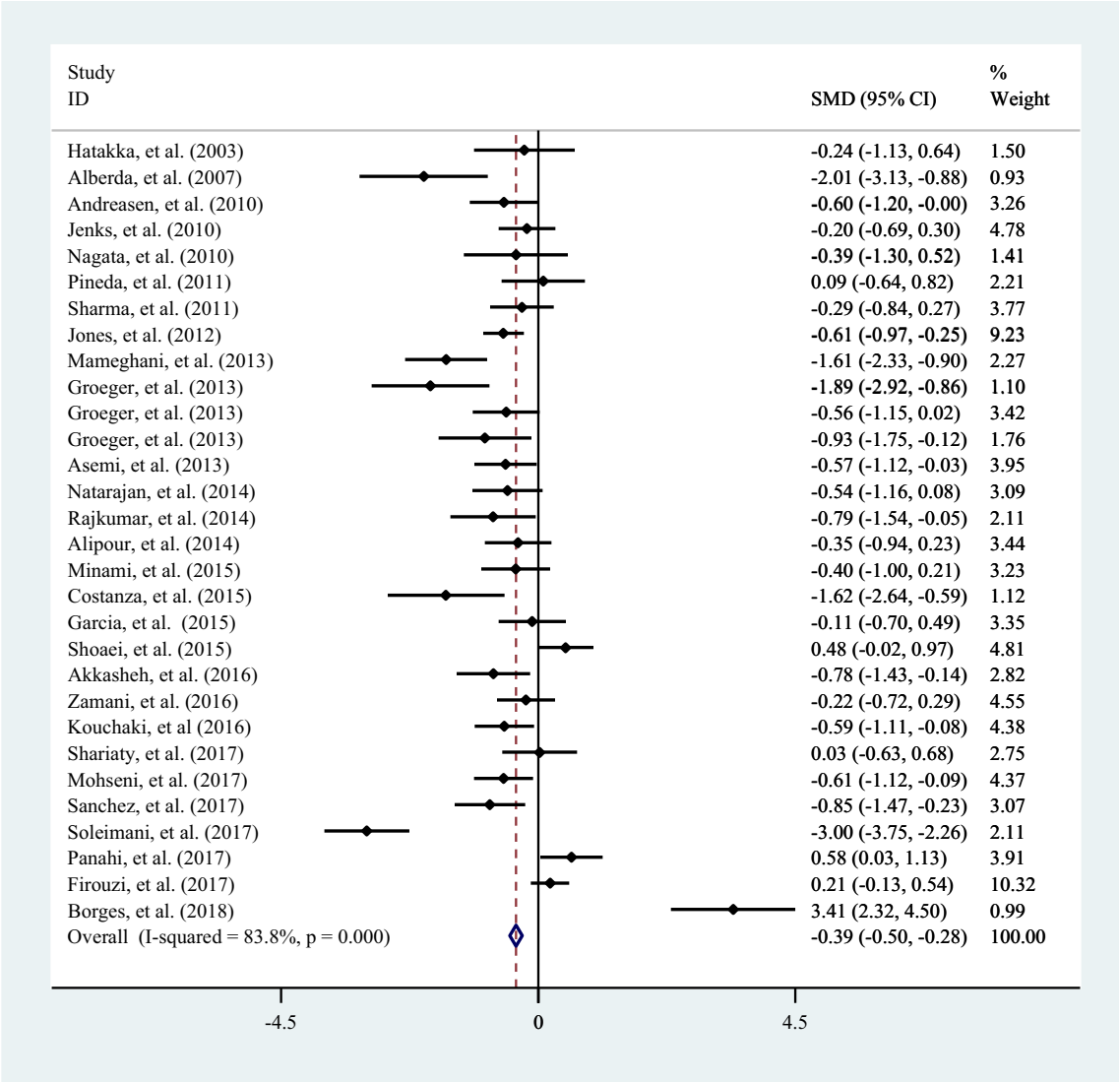

Fig. 1 Forest plot for the effect of probiotics supplementation on serum hs-CRP concentrations, expressed as the mean differences between the intervention and the control diets. The area of each square is proportional to the inverse of the variance of the SMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from fixed-effects analysis

Table 1 Subgroup analysis for the effect of probiotics supplementation on serum concentrations of CRP and IL-6

Subgroup	Number of effect sizes		Participants, *N*		Effect size (95% CI)		I^2		*P* within[a]		*P* between[a]	
	CRP	IL-6	CRP	IL-6	CRP	IL-6	CRP	IL-6	CRP	IL-6	CRP	IL-6
Overall	31	20	1579	840	−0.33 (−0.44, −0.23)	−0.37 (−0.51, −0.24)	84.2	69.7	< 0.001	< 0.001	–	–
Participants' age												
Adult	14	13	521	585	−0.31 (−0.48, −0.14)	−0.34 (−0.50, −0.17)	85.4	74.5	< 0.001	< 0.001	0.04	0.40
Adult + elderly	16	7	1038	255	−0.33 (−0.46, −0.20)	−0.47 (−0.72, −0.21)	84.1	59.6	< 0.001	0.02		
NR	1	–	20	–	−1.62 (−2.64, −0.59)	–	–	–	–	–		
Supplement dosage												
< 10 CFU/day	12	10	668	93	−0.45 (−0.61, −0.29)	−0.49 (−0.68, −0.31)	83.5	55.4	< 0.001	0.01	< 0.001	0.07
10–100 CFU/day	15	8	802	282	−0.12 (−0.26, 0.02)	−0.14 (−0.39, 0.10)	83.4	77.4	< 0.001	< 0.001		
≥ 100 CFU/day	3	2	89	465	−1.36 (−1.83, −0.89)	−0.47 (−0.89, −0.05)	49.8	83.9	0.13	0.01		
NR	1	–	20	–	−1.62 (−2.64, −0.23)	–	–	–	–	–		
Study duration												
< 10 week	18	15	837	674	−0.48 (−0.62, −0.34)	−0.39 (−0.55, −0.24)	71.4	70.2	< 0.001	< 0.001	< 0.01	0.60
≥ 10 week	13	5	742	166	−0.16 (−0.32, −0.01)	−0.30 (−0.62, 0.01)	90.1	74.1	< 0.001	< 0.01		
Outcome assessment												
Immunoassay	18	3	1129	96	−0.27 (−0.39, −0.15)	−0.50 (−0.93, −0.08)	87.7	81.6	< 0.001	< 0.01	0.02	0.18
Electrochemiluminescence	3	10	86	419	−0.90 (−1.33, −0.47)	−0.44 (−0.64, −0.24)	58.4	64.6	0.09	< 0.01		
Bead assay	–	5	–	274	–	−0.34 (−0.59, −0.10)	–	81.1	–	< 0.001		
NR	10	2	364	51	−0.39 (−0.61, −0.18)	0.20 (−0.36, 0.75)	77.0	0.0	< 0.001	0.57		
Health condition												
Healthy	3	3	201	206	−0.59 (−0.87, −0.31)	−0.33 (−0.61, −0.05)	0.0	90.0	0.70	< 0.001	< 0.001	0.71
Gastrointestinal disease	3	6	116	218	−0.73 (−1.11, −0.34)	−0.41 (−0.69, −0.14)	73.0	79.0	0.02	< 0.001		
Skeletal disorders	6	4	267	161	−0.26 (−0.51, −0.02)	−0.44 (−0.76, −0.12)	0.0	0.0	0.83	0.44		
Metabolic diseases	6	1	496	45	−0.01 (−0.19, 0.17)	−0.17 (−0.76, 0.42)	74.8	–	< 0.01	–		
Allergy an autoimmune diseases	3	1	105	26	0.01 (−0.40, 0.42)	0.25 (−0.52, 1.02)	80.2	–	< 0.01	–		
Renal diseases	4	2	171	72	−0.51 (−0.87, −0.15)	−0.52 (−1.01, −0.03)	96.9	90.9	< 0.001	< 0.01		
Critical illness	2	–	59	–	−1.73 (−2.33, −1.12)	–	0.0	–	0.56	–		
Other diseases	4	3	164	112	−0.60 (−0.91, −0.28)	−0.43 (−0.81, −0.06)	55.9	0.0	0.07	0.53		
Participants' sex												
Male	3	1	124	45	−0.03 (−0.40, 0.34)	−0.17 (−0.76, 0.42)	77.4	–	0.01	–	0.03	0.24
Female	3	4	159	183	−0.07 (−0.39, 0.24)	−0.18 (−0.48, 0.12)	76.0	82.5	0.01	< 0.01		
Both genders	25	15	1296	612	−0.40 (−0.51, −0.28)	−0.45 (−0.61, −0.28)	85.5	67.2	< 0.001	< 0.001		
Probiotic type												
Lactobacillus	5	10	268	448	−0.46 (−0.70, −0.21)	−0.37 (−0.56, −0.18)	0.0	39.6	0.49	0.09	0.01	0.34
Bifidobacter	6	4	203	140	−0.72 (−1.01, −0.43)	−0.60 (−0.95, −0.25)	30.9	74.0	0.20	< 0.01		
Saccharomyces	2	1	64	44	−0.48 (−1.00, 0.03)	−0.52 (−1.12, 0.08)	84.1	–	0.01	–		
Different types	18	5	1044	208	−0.22 (−0.34, −0.09)	−0.20 (−0.49, 0.08)	89.5	87.8	< 0.001	< 0.001		

[a]*P* values were obtained by fixed-effect analysis

the effect of probiotic supplementation was seen only in studies that were performed in both gender and it was not significant in studies that confined the participants to males or females.

Findings on the effect of probiotics on serum IL-6

Based on 16 studies with 20 effect sizes, a significant reduction in serum IL-6 was found after probiotic supplementation [SMD −0.37; 95% CI (−0.51, −0.24), $I^2 = 69.7\%$] (Fig. 2). A significant between-study heterogeneity was seen; however, participants' age and sex, supplement dose, study duration, and method of outcome assessment did not explain the heterogeneity (Table 1). Health status of participants as well as type of bacteria used made the between-study heterogeneity disappeared. In all above-mentioned subgroups, the significant effect of probiotics on serum IL-6 concentrations was still significant; however, the effect was not significant among studies that used a dosage of 10–100 CFU/day, those that were performed on women as well as those that used multiple types of bacteria in one study.

Findings on the effect of probiotics on TNF-a

Pooling effect sizes from 18 studies with 21 effect sizes, we found a significant reduction in serum TNF-a concentrations after probiotic supplementation [SMD −0.21; 95% CI (−0.34, −0.08), $I^2 = 85.5\%$] (Fig. 3). Due to heterogeneity, we conducted subgroup analysis to find possible sources (Table 2). Participants' age and sex as well as study duration did not explain the between-study heterogeneity. In all above-mentioned subgroups, except for studies with an intervention duration of ≥ 10 weeks, the effect of probiotic supplementation on TNF-a was still significant. Dosages of probiotic supplements, method of outcome assessment, health status of participants, and type of bacteria could

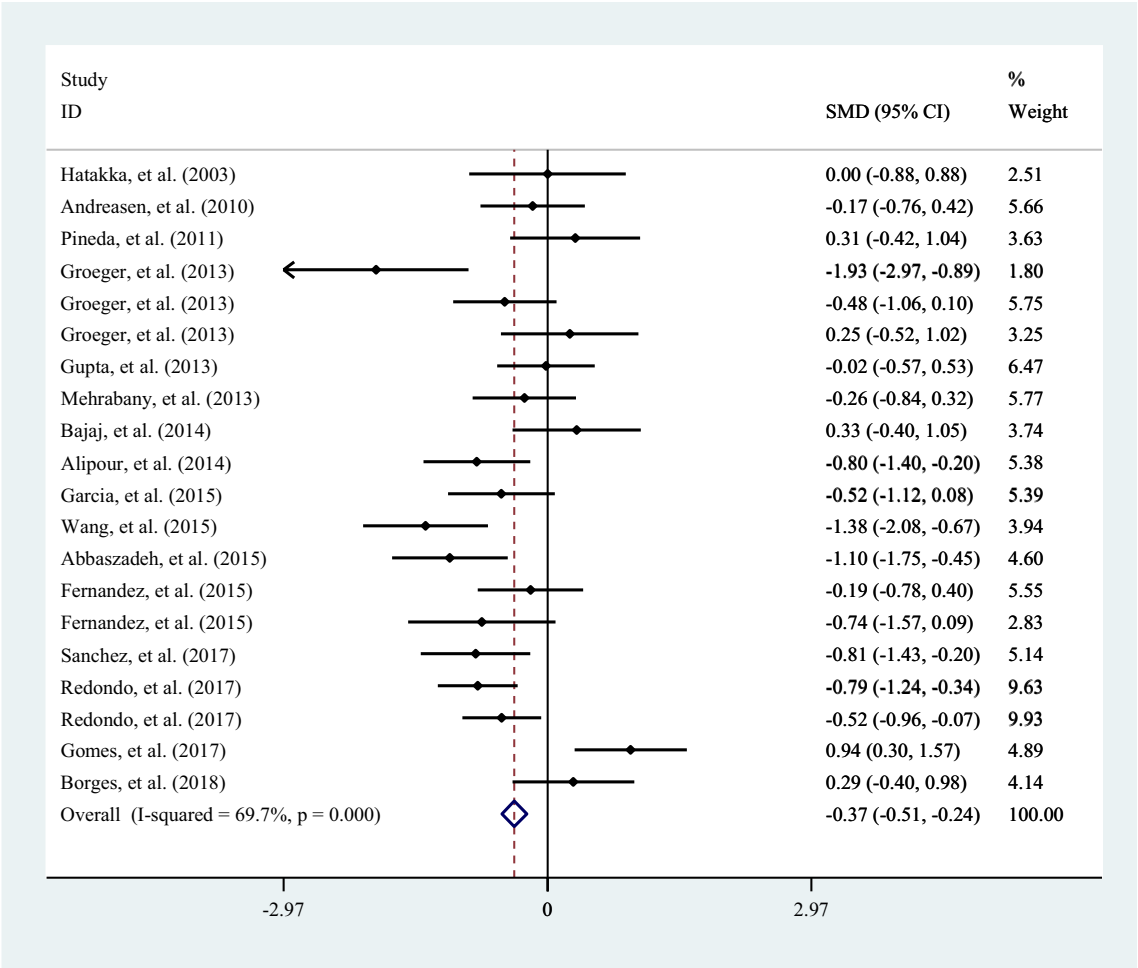

Fig. 2 Forest plot for the effect of probiotics supplementation on serum IL-6 concentrations, expressed as the mean differences between the intervention and the control diets. The area of each square is proportional to the inverse of the variance of the SMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from fixed-effects analysis

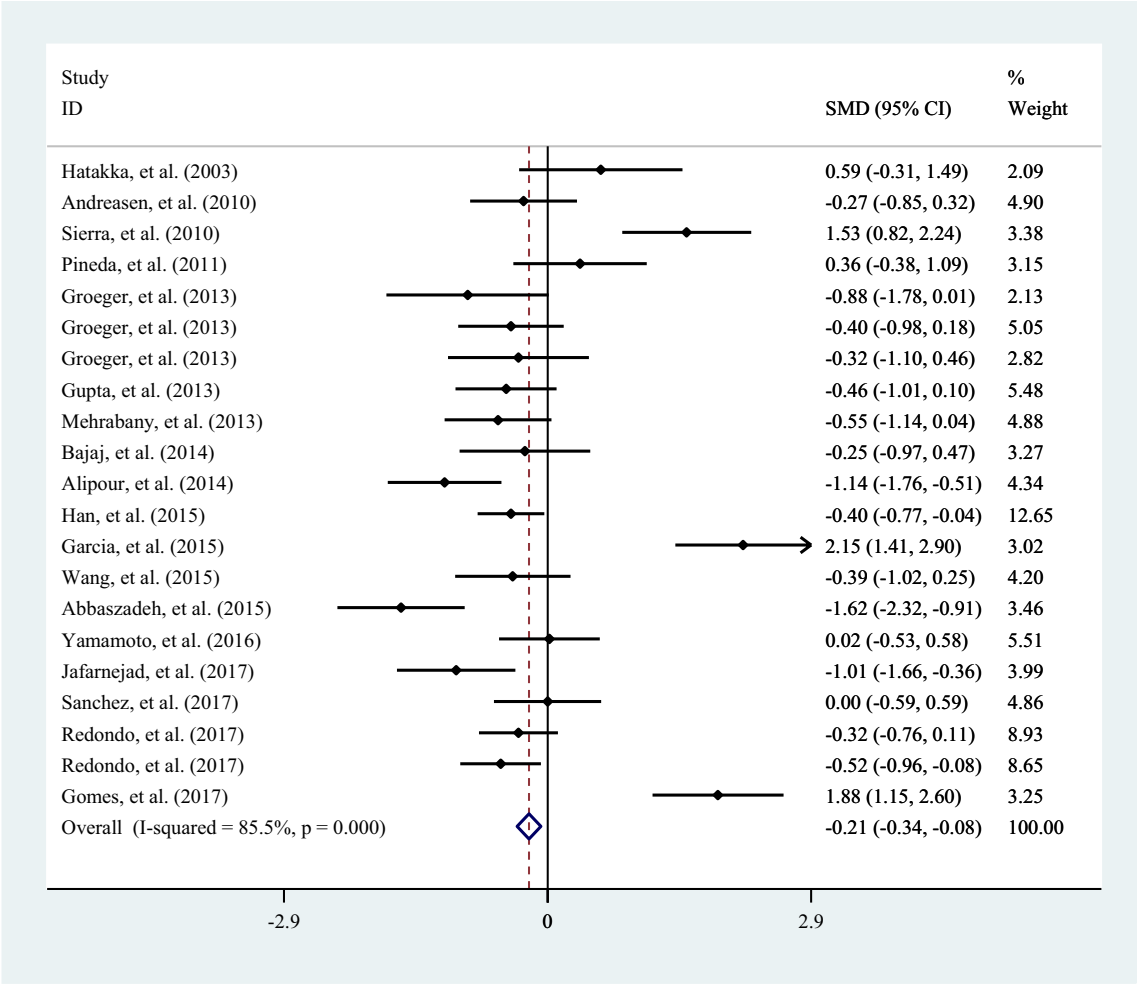

Fig. 3 Forest plot for the effect of probiotics supplementation on serum TNF-a concentrations, expressed as the mean differences between the intervention and the control diets. The area of each square is proportional to the inverse of the variance of the SMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from fixed-effects analysis

provide some explanations for the heterogeneity. In these analyses, we found that the effect of probiotics on TNF-a was not significant among studies that used probiotics at the dosages of < 1 and 10–100 CFU/day. In addition, the effect of supplementation was not significant among studies that were done on healthy participants and those with allergy and autoimmune diseases.

Findings on the effect of probiotics on serum Interleukin-10 (IL-10)

Pooling effect sizes from 11 studies with 12 effect sizes, a significant increase in IL-10 concentrations was seen following probiotic supplementation [SMD 0.21; 95% CI (0.04, 0.38), $I^2 = 48.5\%$] (Fig. 4). However, in the subgroup analysis, the effect was not significant among studies conducted exclusively on adults as well as those performed on both genders, studies that used bifidobacter, those that used the dosage of ≥ 1 CFU/day of probiotic supplement, and those that used bead assay for outcome assessment (Table 2). In addition, no significant effect was seen among studies that were performed on healthy participants or subjects with gastrointestinal diseases.

Findings on the effect of probiotics on serum interleukin-1 beta (IL-1B)

Combining ten effect sizes from nine studies, we failed to find a significant effect of probiotic supplementation on IL-1B concentrations [SMD −0.17; 95% CI (−0.37, 0.02), $I^2 = 80.7\%$] (Fig. 5). A significant between-study heterogeneity was seen. Subgroup analysis based on participants' age and gender, duration of study, and health status of participants did not explain the heterogeneity (Table 3). When the analysis was done stratified by supplement dosage, the between-study heterogeneity was disappeared for studies

Table 2 Subgroup analysis for the effect of probiotics supplementation on serum concentrations of TNF-a and IL-10

Subgroup	Number of effect sizes		Participants, *N*		Effect size (95% CI)		I^2		*P* within[a]		*P* between[a]	
	TNF-a	IL-10	TNF-a	IL-10	TNF-a	IL-10	TNF-a	IL-10	TNF-a	IL-10	TNF-a	IL-10
Overall	21	12	987	545	−0.21 (−0.34, −0.08)	0.21 (0.04, 0.38)	85.5	48.5	< 0.001	0.03	–	–
Participants' age												
Adult	13	9	592	424	−0.16 (−0.33, 0.01)	0.16 (−0.03, 0.35)	84.5	57.2	< 0.001	0.01	0.40	0.27
Adult + elderly	7	3	395	121	−0.27 (−0.48, −0.07)	0.39 (0.03, 0.75)	88.2	0.0	< 0.001	0.47		
Supplement dosage												
< 1 CFU/day	4	3	176	132	0.26 (−0.07, 0.59)	0.67 (0.31, 1.02)	95.3	22.7	< 0.001	0.27	< 0.001	0.01
1–10 CFU/day	6	5	302	261	−0.39 (−0.62, −0.17)	0.11 (−0.14, 0.35)	37.5	49.0	0.15	0.09		
10–100 (≥ 10) CFU/day	7	4	249	152	0.05 (−0.21, 0.31)	0.02 (−0.30, 0.34)	82.6	0.0	< 0.001	0.47		
≥ 100 CFU/day	2	–	93	–	−0.91 (−1.34, −0.47)	–	84.4	–	0.01	–		
NR	2	–	167	–	−0.28 (−0.58, 0.03)	–	36.3	–	0.21	–		
Study duration												
< 10 week	15	8	763	412	−0.31 (−0.45, −0.16)	0.18 (−0.01, 0.38)	83.7	54.8	< 0.001	0.03	< 0.01	0.52
≥ 10 week	6	4	224	133	0.15 (−0.13, 0.43)	0.31 (−0.04, 0.66)	88.6	45.2	< 0.001	0.14		
Outcome assessment												
Immunoassay	13		634	7	−0.23 (−0.40, −0.07)	0.39 (0.16, 0.63)	87.7	61.0	< 0.001	0.01	0.28	0.09
Electrochemiluminescence	3		96	–	−0.48 (−0.89, −0.07)	–	0.0	–	0.60	–		
Bead assay	3		206	3	−0.06 (−0.35, 0.22)	0.03 (−0.25, 0.30)	94.0	0.0	< 0.001	0.52		
NR	2		51	2	0.08 (−0.49, 0.64)	−0.02 (−0.58, 0.53)	50.7	0.0	0.15	0.92		
Health condition												
Healthy	4	4	246	246	0.16 (−0.10, 0.43)	0.18 (−0.07, 0.43)	94.0	69.0	< 0.001	0.02	< 0.001	0.09
Gastrointestinal disease	6	2	306	74	−0.50 (−0.73, −0.27)	−0.20 (−0.66, 0.26)	64.1	0.0	0.01	0.47		
Skeletal disorders	6	3	231	113	−0.48 (−0.75, −0.21)	0.40 (0.02, 0.77)	71.0	0.0	< 0.01	0.44		
Metabolic diseases	1	–	45	–	−0.27 (−0.85, 0.32)	–	–	–	–	–		
Allergy an autoimmune diseases	2	1	76	44	−0.09 (−0.55, 0.36)	0.12 (−0.48, 0.71)	0.0	–	0.48	–		
Renal diseases	1	1	39	39	−0.39 (−1.02, 0.25)	0.99 (0.32, 1.65)	–	–	–	–		
Other diseases	1	1	44	29	2.15 (1.41, 2.90)	0.05 (−0.68, 0.78)	–	–	–	–		
Participants' sex												
Male	1	–	45	–	−0.27 (−0.85, 0.32)	–	–	–	–	–	0.48	0.12
Female	5	3	224	135	−0.35 (−0.63, −0.07)	0.44 (0.10, 0.79)	91.5	0.0	< 0.001	0.73		
Both genders	15	9	718	410	−0.16 (−0.31, −0.01)	0.14 (−0.06, 0.33)	84.3	56.6	< 0.001	0.01		
Probiotic type												
Lactobacillus	10	7	470	346	−0.19 (−0.38, −0.01)	0.22 (0.00, 0.43)−	78.0	52.0	< 0.001	0.05	< 0.001	0.12
Bifidobacter	4	2	140	88	−0.32 (−0.66, 0.01)	0.11 (−0.53, 0.31)	0.0	10.9	0.43	0.28		
Saccharomyces	1	1	44	29	2.15 (1.41, 2.90)	0.05 (−0.68, 0.78)	–	–	–	–		

Table 2 (continued)

Subgroup	Number of effect sizes		Participants, *N*		Effect size (95% CI)		I^2		*P* within[a]		*P* between[a]	
	TNF-a	IL-10	TNF-a	IL-10	TNF-a	IL-10	TNF-a	IL-10	TNF-a	IL-10	TNF-a	IL-10
Different types	6	2	333	82	−0.39 (−0.61, −0.16)	0.62 (0.17, 1.07)	90.6	51.5	< 0.001	0.15		

[a]*P* values were obtained by fixed-effect analysis

that used < 1 CFU/day of bacteria ($I^2 = 19.2\%$). The effect of supplementation was non-significant in all subgroups, except for studies that were performed on adults and on females, in which a significant reduction in serum IL-1B concentrations was found after supplementation. In addition, probiotic supplementation at the dosages of < 1 or ≥ 1 CFU/day resulted in a significant reduced concentrations of serum IL-1B.

Findings on the effect of probiotics on serum IL-12

When we combined data from eight studies with nine effect sizes, a significant reduction in serum IL-12 concentrations was found after probiotic supplementation [SMD −0.47; 95% CI (−0.67, −0.27), $I^2 = 85.2\%$] (Fig. 6). To find possible sources of between-study heterogeneity, we did subgroup analysis, but participants' age, gender, and health status and supplement dosage did not provide any explanation for this heterogeneity (Table 3). However, heterogeneity was disappeared in studies with a duration of ≥ 10 weeks.

Findings on the effect of probiotics on other cytokines

Pooling five effect sizes from four studies, no significant effect of probiotic supplementation on serum IL-8 [SMD −0.01; 95% CI (−0.30, 0.28), $I^2 = 73.0\%$] and interferon-gama (IFN-g) concentrations was found [SMD −0.08; 95% CI (−0.31, 0.15), $I^2 = 0.0\%$] (Fig. 7a, b). In addition, we failed to find a significant effect of probiotic supplementation on serum levels of IL-17 based on three studies [SMD 0.06; 95% CI (−0.34, 0.46), $I^2 = 0.0\%$] (Fig. 7c). However, probiotic supplementation resulted in a lower concentration on IL-4 concentrations compared to placebo [SMD −0.48; 95% CI (−0.76, −0.20), $I^2 = 0.0\%$] (Fig. 7d).

Discussion

In the current study, we found a significant reduction in serum hs-CRP, TNF-a, IL-6, IL-12, and IL-4 concentrations after probiotic supplementation. In addition, serum concentrations of IL-10 were significantly increased following probiotic supplementation. However, no significant effects of probiotic supplementation on IL-1B, IL-8, IFN-g, and IL-17 concentrations were found in our meta-analysis.

We found a significant reduction in some inflammatory cytokines including hs-CRP, TNF-a, IL-6, IL-12, and IL-4 after probiotic supplementation. A meta-analysis of RCTs on the effect of probiotic supplementation on serum CRP concentrations, published in 2017, showed a significant reduction in serum levels after probiotic intake [59]. Probiotic supplementation resulted in reduced TNF-a concentrations in patients with non-alcoholic fatty liver disease, as found in

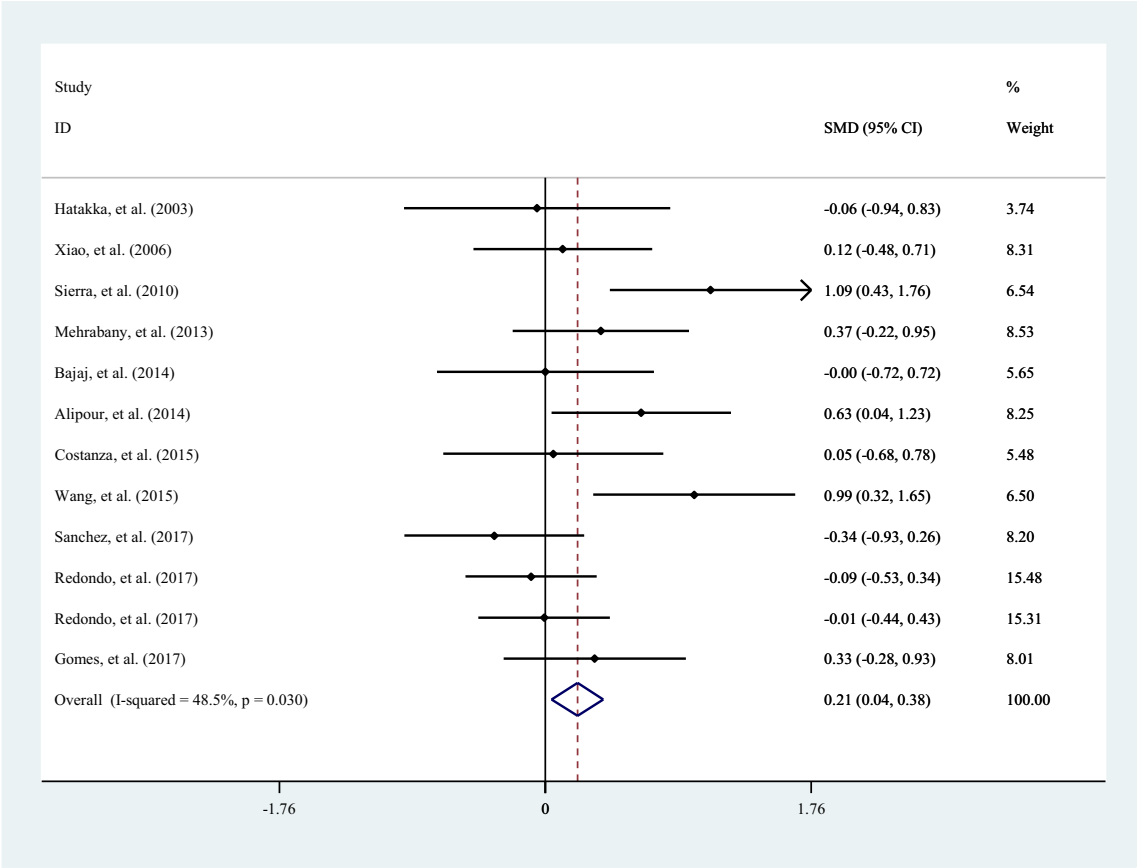

Fig. 4 Forest plot for the effect of probiotics supplementation on serum IL-10 concentrations, expressed as the mean differences between the intervention and the control diets. The area of each square is proportional to the inverse of the variance of the SMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from fixed-effects analysis

a meta-analysis [60]. Among patients with colorectal cancer, probiotic supplementation led to reduced serum concentrations of CRP, but changes in serum levels of IL-6 were not significant [61]. However, sample sizes of included studies in that meta-analysis were small. In addition, probiotic supplementation did not change serum concentrations of inflammatory cytokines including TNF-α, IL-1β, IL-6, IL-10, and IL-12 in patients with rheumatoid arthritis [62]. However, only four studies were included in that study. Although a significant reduction in IL-4 concentrations after probiotic supplementation was found in our study, the number of included studies in this area was low. Further studies are needed to reach a firm conclusion.

The effect of probiotic supplementation on hs-CRP concentrations was not significant in studies conducted in patients with metabolic diseases. Chronic low-grade inflammation plays a pivotal role in the pathogenesis of these conditions [63]. Most studies performed on these patients did not consider baseline status of inflammation in their analyses. Moreover, due to high concentrations of inflammatory cytokines in these patients [63], it seems that interventions with higher doses of probiotics for longer periods would be required to observe the affect on inflammation. In this meta-analysis, the effect of probiotics on serum CRP and TNF-a concentrations was not significant among patients with allergy and autoimmune diseases. In addition, no significant effect of probiotic supplementation was seen on TNF-a concentrations among studies conducted on healthy participants. However, studies in these areas were relatively rare and between-study heterogeneity was also high. Probiotic supplementation at a dose of 10–100 CFU/day did not significantly change serum concentrations of CRP, TNF-a, and IL-6. This was also the case with a dosage of < 1 CFU/day for CRP concentrations. Different responses to probiotic supplementation in different health conditions might be due to changes in gut microbiota, in particular due to the severity and direction of immune system stimulation through the gut-associated lymphoid tissue (GALT) [64, 65]. Data for the effects of each strain of probiotics on serum concentrations of cytokines were insufficient, and a considerable number of included studies had used multiple strains. However,

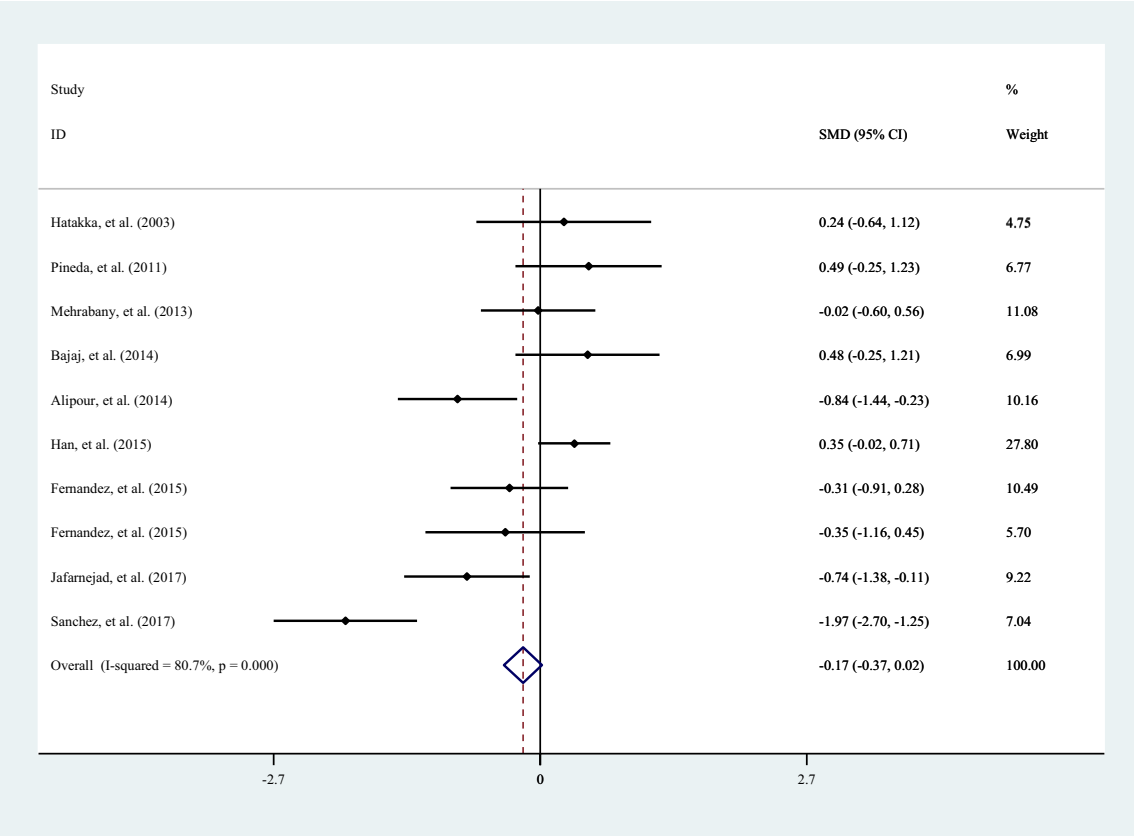

Fig. 5 Forest plot for the effect of probiotics supplementation on serum IL-1B concentrations, expressed as the mean differences between the intervention and the control diets. The area of each square is proportional to the inverse of the variance of the SMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from fixed-effects analysis

our subgroup analysis showed that bifidobacter had higher impact on hs-CRP and IL-6 levels compared to lactobacillus, while saccharomyces did not have a significant effect. Due to the limited number of studies in this regard, further studies are needed to confirm these findings and to explore probable mechanisms of action.

A significant increase in serum IL-10 concentrations was seen after probiotic supplementation. In a recent meta-analysis on the effect of probiotic administration on hs-CRP concentrations, the investigators did not find a significant effect of supplementation on IL-10 levels [59]. However, the main aim of that meta-analysis was focusing on serum hs-CRP levels and they did not include all studies that examined the effect on IL-10 concentrations. In addition, in another meta-analysis on 4 published papers on the effect of probiotic supplementation on serum concentrations of IL-10 in patients with rheumatoid arthritis, no significant effect was reported [62]. IL-10 has anti-inflammatory properties [66]. Several studies in animal models have shown that IL-10 concentrations are increased after probiotic consumption [67, 68]. However, as the significant effect of probiotic supplementation on IL-10 concentrations disappeared in subgroup analyses, it seems that further studies are needed to shed light in this issue.

The effect of probiotic supplementation on IL-1B, IL-8, IFN-g, and IL-17 concentrations was not significant in our meta-analysis. Findings from a meta-analysis on the effect of probiotics on cytokines in patients with rheumatoid arthritis revealed no significant effect on serum levels of IL-1B [62]. Further studies using different doses of probiotic supplements are recommended for the future investigations.

Gut is the main reservoir of antigens [69]. It is involved in immune function [61]. The role of gut in inflammation might be partially due to the presence of GALT, which is a lymphoid organ containing the majority of total lymphocytes in body [70]. Previous studies have shown that administration of probiotics can modulate gut immune function by restoring normal function of mucosal barrier [71]. In addition, probiotics may skew immune responses towards immunoregulation by inducing T-reg cells [72]. Lack of microbial antigens-induced immune stimulation in gut deviates cytokine profile from Th1- to Th2-related types [73]. Therefore, it is assumed that consumption of probiotics will alter microbial population in gut and subsequently regulate

Table 3 Subgroup analysis for the effect of probiotics supplementation on serum concentrations of IL-1B and IL-12

Subgroup	Number of effect sizes		Participants, *N*		Effect size (95% CI)		I^2		*P* within[a]		*P* between[2]	
	IL-1B	IL-12	IL-1B	IL-12	IL-1B	IL-12	IL-1B	IL-12	IL-1B	IL-12	IL-1B	IL-12
Overall	10	9	442	439	−0.17 (−0.37, 0.02)	−0.47 (−0.67, −0.27)	80.7	85.2	<0.001	<0.001	–	–
Participants' age												
Adult	3	5	95	268	−0.50 (−0.94, −0.06)	−0.43 (−0.68, −0.18)	92.1	75.3	<0.001	<0.01	0.11	0.60
Adult + elderly	7	4	347	171	−0.10 (−0.31, 0.12)	−0.54 (−0.86, −0.21)	67.9	92.0	<0.01	<0.001		
Supplement dosage												
< 1 CFU/day	4	3	160	132	−0.37 (−0.69, −0.06)	−0.84 (−1.22, −0.46)	19.2	92.7	0.29	<0.001	<0.01	<0.01
≥ 1 CFU/day	5	5	165	257	−0.37 (−0.70, −0.04)	−0.45 (−0.70, −0.20)	87.6	75.9	<0.001	<0.01		
NR	1	1	117	50	0.35 (−0.02, 0.71)	0.24 (−0.32, 0.79)	–	–	–	–		
Study duration												
< 10 week	7	6	351	339	−0.19 (−0.40, 0.03)	−0.72 (−0.94, −0.49)	84.9	85.1	<0.001	<0.001	0.76	<0.001
≥ 10 week	3	3	91	100	−0.12 (−0.54, 0.31)	0.31 (−0.09, 0.70)	71.2	0.0	0.03	0.53		
Health condition												
Healthy	–	3	–	203	–	−0.32 (−0.60, −0.04)	–	75.8	–	0.01	0.41	<0.01
Gastrointestinal	3	1	191	44	−0.02 (−0.32, 0.28)	−1.26 (−1.91, −0.61)	65.3	–	<0.001	–		
disease	5	4	183	142	−0.26 (−0.56, 0.03)	−0.77 (−1.14, −0.41)	94.0	90.0	0.02	<0.001		
Skeletal disorders	–	1	–	50	–	0.24 (−0.32, 0.79)	–	–	–	–		
Allergy and auto-immune diseases	2	–	68	–	−0.33 (−0.81, 0.15)	–	0.0	–	0.93	–		
Other diseases												
Participants' sex												
Female	3	2	133	94	−0.51 (−0.86, −0.16)	−1.57 (−2.04, −1.10)	54.2	57.5	0.11	0.12	0.02	<0.001
Both genders	7	7	309	345	−0.03 (−0.26, 0.21)	−0.24 (−0.46, −0.02)	83.8	77.4	<0.001	<0.001		

[a]*P* values were obtained by fixed-effect analysis

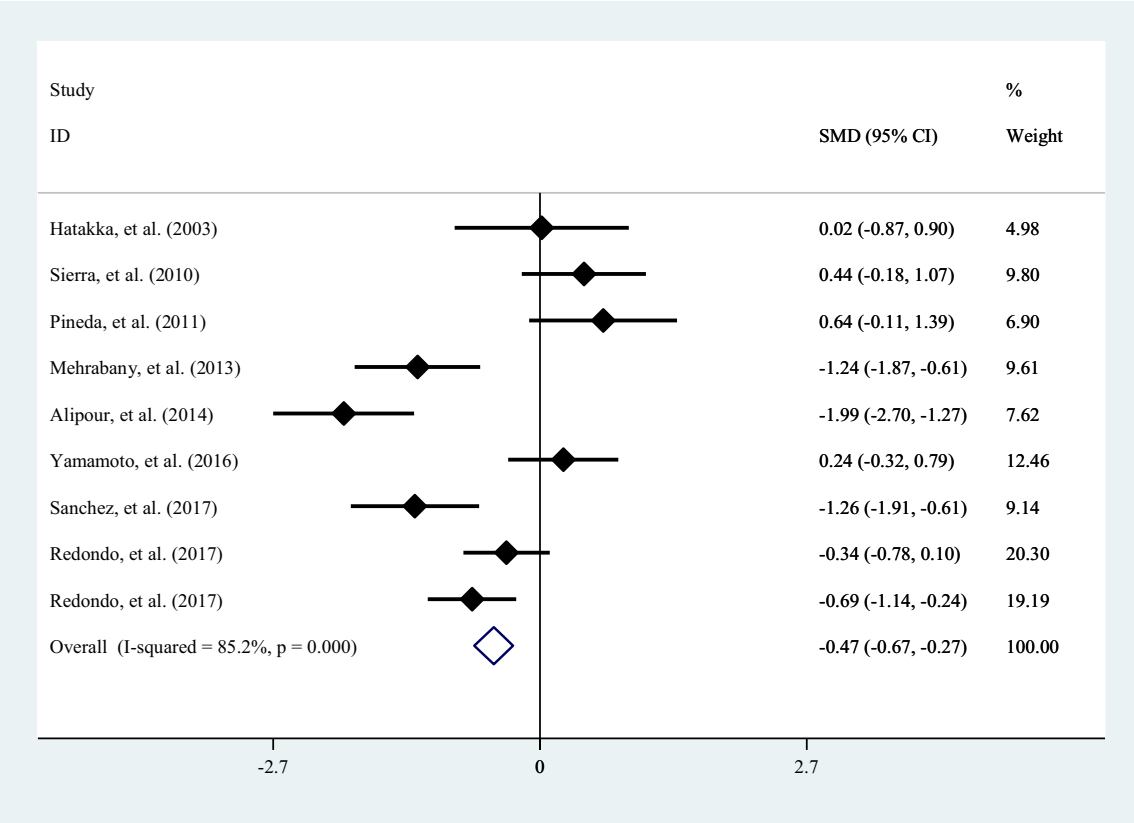

Fig. 6 Forest plot for the effect of probiotics supplementation on serum IL-12 concentrations, expressed as the mean differences between the intervention and the control diets. The area of each square is proportional to the inverse of the variance of the SMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from fixed-effects analysis

secretion of inflammatory cytokines towards the reduced body inflammation.

This is the first comprehensive meta-analysis on the effect of probiotics on various inflammatory cytokines. All studies we included were RCTs. Some limitations should be taken into account. Probiotics were used in different dosages in included studies. Moreover, different strains of probiotics were used. We tried to take in account this problem using subgroup analysis based on probiotic type. The wide ranges of intervention periods were another possible source of bias in this meta-analysis. In addition, participants in included studies were in different physiological status. Therefore, future studies should be separately conducted in participants with different health conditions. Furthermore, most included studies did not adjust their findings for the baseline levels of cytokines.

Conclusion

In conclusion, we found a significant reduction in serum concentrations of pro-inflammatory cytokines, including hs-CRP, TNF-a, IL-6, IL-12, and IL-4 after probiotic supplementation. Moreover, serum concentrations of IL-10, as an anti-inflammatory agent, were significantly increased. The effects of probiotic supplementation on serum IL-1B, IL-8, IFN-g, and IL-17 concentrations were not significant. Therefore, it seems that intake of probiotics might considerably reduce inflammation in humans. Further studies measuring the effects of probiotics on serum concentrations of other inflammatory biomarkers are needed to confirm our conclusion.

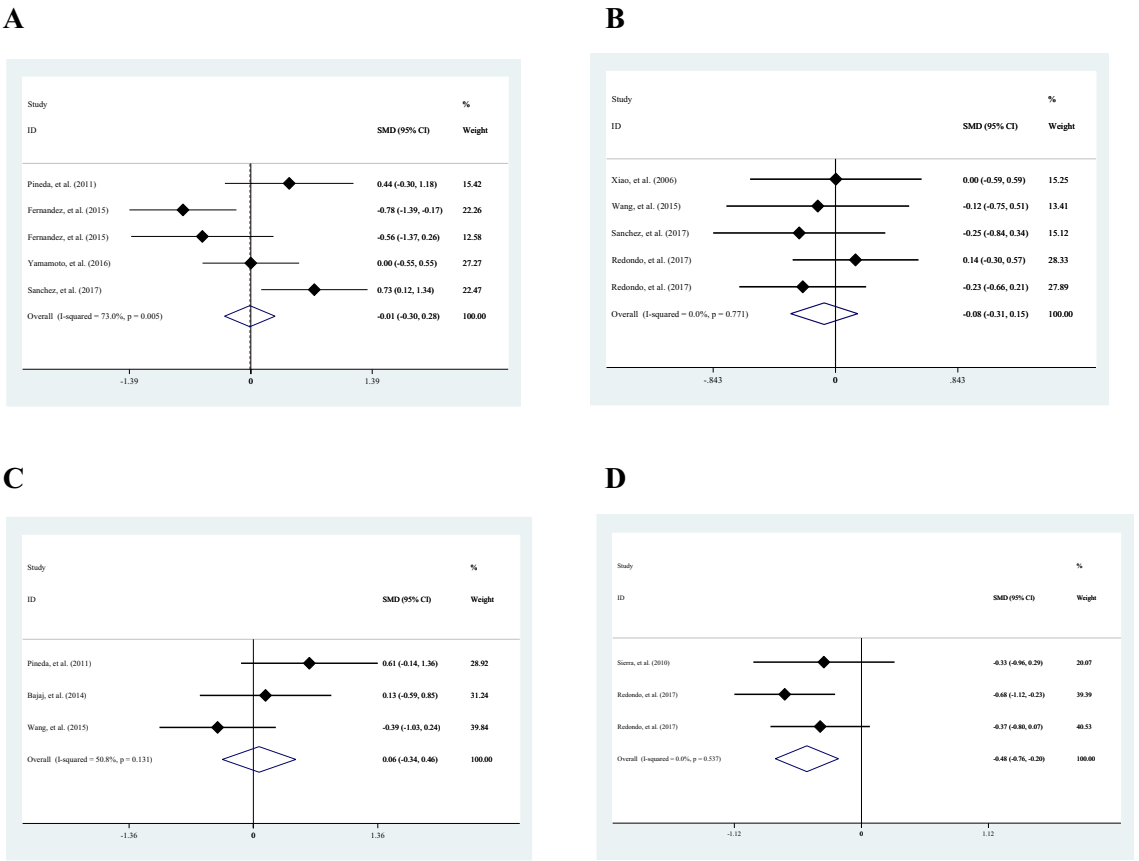

Fig. 7 Forest plot for the effect of probiotics supplementation on serum IL-8 (**a**), IFN-g (**b**), IL-17 (**c**), and IL-4 (**d**) concentrations, expressed as the mean differences between the intervention and the control diets. The area of each square is proportional to the inverse of the variance of the SMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from fixed-effects analysis

Author contributions AM, BL, and AE designed research; AM, SMM, AS, ASM, and MP conducted research; AM analyzed data; AM and AE wrote the paper; and AE had primary responsibility for final content. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

References

1. Robertson CM, Coopersmith CM (2006) The systemic inflammatory response syndrome. Microbes Infect 8(5):1382–1389
2. Huang Y, Chen Z (2016) Inflammatory bowel disease related innate immunity and adaptive immunity. Am J Transl Res 8(6):2490
3. Pradhan A (2007) Obesity, metabolic syndrome, and type 2 diabetes: inflammatory basis of glucose metabolic disorders. Nutr Rev 65(suppl_3):S152–S156
4. Guarner V, Rubio-Ruiz ME (2015) Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease. Interdiscip Top Gerontol 40:99–106
5. Başaranoğlu M, Örmeci N (2014) Nonalcoholic fatty liver disease: diagnosis, pathogenesis, and management. Turk J Gastroenterol 25:127–132
6. Speer K, Upton D, Semple S, McKune A (2018) Systemic low-grade inflammation in post-traumatic stress disorder: a systematic review. J Inflamm Res 11:111
7. Ashtary-Larky D, Lamuchi-Deli N, Milajerdi A, Salehi MB, Alipour M, Kooti W, Ashtary-Larky P, Alamiri F, Sheikhi A, Afrisham R (2017) Inflammatory and biochemical biomarkers in response to high intensity resistance training in trained and untrained men. Asian J Sports Med 8(2):1A–1A
8. Kaluza J, Harris H, Melhus H, Michaëlsson K, Wolk A (2018) Questionnaire-based anti-inflammatory diet index as a predictor of low-grade systemic inflammation. Mary Ann Liebert, Inc., New Rochelle
9. Ozawa M, Shipley M, Kivimaki M, Singh-Manoux A, Brunner EJ (2017) Dietary pattern, inflammation and cognitive decline: the Whitehall II prospective cohort study. Clin Nutr 36(2):506–512
10. McLoughlin RF, Berthon BS, Jensen ME, Baines KJ, Wood LG (2017) Short-chain fatty acids, prebiotics, synbiotics, and systemic inflammation: a systematic review and meta-analysis. Am J Clin Nutr 106(3):930–945
11. Li M, van Esch BC, Wagenaar GT, Garssen J, Folkerts G, Henricks PA (2018) Pro-and anti-inflammatory effects of short chain fatty acids on immune and endothelial cells. Eur J Pharmacol 831:52–59

12. Campbell AW (2016) Inflammation and a solution: probiotics. Altern Ther Health Med 22(5):8
13. Wang Z-J, Chen X-F, Zhang Z-X, Li Y-C, Deng J, Tu J, Song Z-Q, Zou Q-H (2017) Effects of anti-*Helicobacter pylori* concomitant therapy and probiotic supplementation on the throat and gut microbiota in humans. Microb Pathog 109:156–161
14. Goldin B, Gorbach S (2008) Clinical indications for probiotics: an overview. Clin Infect Dis 46(Supplement_2):S96–S100
15. Kaur IP, Kuhad A, Garg A, Chopra K (2009) Probiotics: delineation of prophylactic and therapeutic benefits. J Med Food 12(2):219–235
16. Alberda C, Gramlich L, Meddings J, Field C, McCargar L, Kutsogiannis D, Fedorak R, Madsen K (2007) Effects of probiotic therapy in critically ill patients: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr 85(3):816–823
17. Han SH, Suk KT, Kim DJ, Kim MY, Baik SK, Kim YD, Cheon GJ, Choi DH, Ham YL, Shin DH (2015) Effects of probiotics (cultured *Lactobacillus subtilis*/*Streptococcus faecium*) in the treatment of alcoholic hepatitis: randomized-controlled multicenter study. Eur J Gastroenterol Hepatol 27(11):1300–1306
18. Pineda Mde L, Thompson SF, Summers K, de Leon F, Pope J, Reid G (2011) A randomized, double-blinded, placebo-controlled pilot study of probiotics in active rheumatoid arthritis. Med Sci Monit 17(6):CR347–C354
19. Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, Puri P, Sterling RK, Luketic V, Stravitz RT, Siddiqui MS, Fuchs M, Thacker LR, Wade JB, Daita K, Sistrun S, White MB, Noble NA, Thorpe C, Kakiyama G, Pandak WM, Sikaroodi M, Gillevet PM (2014) Randomised clinical trial: Lactobacillus GG modulates gut microbiome, metabolome and endotoxemia in patients with cirrhosis. Aliment Pharmacol Ther 39(10):1113–1125. https://doi.org/10.1111/apt.12695
20. Maslova E, Bhattacharya S, Lin S-W, Michels KB (2010) Caffeine consumption during pregnancy and risk of preterm birth: a meta-analysis. Am J Clin Nutr 92(5):1120–1132
21. Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, Jafari P, Akbari H, Taghizadeh M, Memarzadeh MR, Asemi Z, Esmaillzadeh A (2016) Clinical and metabolic response to probiotic administration in patients with major depressive disorder: a randomized, double-blind, placebo-controlled trial. Nutrition 32(3):315–320
22. Alipour B, Homayouni-Rad A, Vaghef-Mehrabany E, Sharif SK, Vaghef-Mehrabany L, Asghari-Jafarabadi M, Nakhjavani MR, Mohtadi-Nia J (2014) Effects of *Lactobacillus casei* supplementation on disease activity and inflammatory cytokines in rheumatoid arthritis patients: a randomized double-blind clinical trial. Int J Rheum Dis 17(5):519–527. https://doi.org/10.1111/1756-185x.12333
23. Andreasen AS, Larsen N, Pedersen-Skovsgaard T, Berg RM, Moller K, Svendsen KD, Jakobsen M, Pedersen BK (2010) Effects of *Lactobacillus acidophilus* NCFM on insulin sensitivity and the systemic inflammatory response in human subjects. Br J Nutr 104(12):1831–1838. https://doi.org/10.1017/s0007114510002874
24. Asemi Z, Zare Z, Shakeri H, Sabihi SS, Esmaillzadeh A (2013) Effect of multispecies probiotic supplements on metabolic profiles, hs-CRP, and oxidative stress in patients with type 2 diabetes. Ann Nutr Metab 63(1–2):1–9. https://doi.org/10.1159/000349922
25. Behrouz V, Jazayeri S, Aryaeian N, Zahedi MJ, Hosseini F (2017) Effects of probiotic and prebiotic supplementation on leptin, adiponectin, and glycemic parameters in non-alcoholic fatty liver disease: a randomized clinical trial. Middle East J Dig Dis 9(3):150–157. https://doi.org/10.15171/mejdd.2017.66
26. Borges NA, Carmo FL, Stockler-Pinto MB, de Brito JS, Dolenga CJ, Ferreira DC, Nakao LS, Rosado A, Fouque D, Mafra D (2018) Probiotic supplementation in chronic kidney disease: a double-blind, randomized, placebo-controlled trial. J Ren Nutr 28(1):28–36. https://doi.org/10.1053/j.jrn.2017.06.010
27. Costanza AC, Moscavitch SD, Faria Neto HC, Mesquita ET (2015) Probiotic therapy with *Saccharomyces boulardii* for heart failure patients: a randomized, double-blind, placebo-controlled pilot trial. Int J Cardiol 179:348–350. https://doi.org/10.1016/j.ijcard.2014.11.034
28. Ebrahimi-Mameghani M, Sanaie S, Mahmoodpoor A, Hamishehkar H (2013) Effect of a probiotic preparation (VSL#3) in critically ill patients: a randomized, double-blind, placebo-controlled trial (pilot study). Pak J Med Sci 29(2):490–494
29. Firouzi S, Majid HA, Ismail A, Kamaruddin NA, Barakatun-Nisak MY (2017) Effect of multi-strain probiotics (multi-strain microbial cell preparation) on glycemic control and other diabetes-related outcomes in people with type 2 diabetes: a randomized controlled trial. Eur J Nutr 56(4):1535–1550. https://doi.org/10.1007/s00394-016-1199-8
30. Flichy-Fernández A, Ata-Ali J, Alegre-Domingo T, Candel-Martí E, Ata-Ali F, Palacio J, Peñarrocha-Diago M (2015) The effect of orally administered probiotic *Lactobacillus reuteri*-containing tablets in peri-implant mucositis: a double-blind randomized controlled trial. J Periodontal Res 50(6):775–785
31. Gomes AC, de Sousa RG, Botelho PB, Gomes TL, Prada PO, Mota JF (2017) The additional effects of a probiotic mix on abdominal adiposity and antioxidant status: a double-blind, randomized trial. Obesity (Silver Spring Md) 25(1):30–38. https://doi.org/10.1002/oby.21671
32. Groeger D, O'Mahony L, Murphy EF, Bourke JF, Dinan TG, Kiely B, Shanahan F, Quigley EM (2013) *Bifidobacterium infantis* 35624 modulates host inflammatory processes beyond the gut. Gut Microbes 4(4):325–339. https://doi.org/10.4161/gmic.25487
33. Gupta N, Kumar A, Sharma P, Garg V, Sharma BC, Sarin SK (2013) Effects of the adjunctive probiotic VSL#3 on portal haemodynamics in patients with cirrhosis and large varices: a randomized trial. Liver Int 33(8):1148–1157. https://doi.org/10.1111/liv.12172
34. Hatakka K, Martio J, Korpela M, Herranen M, Poussa T, Laasanen T, Saxelin M, Vapaatalo H, Moilanen E, Korpela R (2003) Effects of probiotic therapy on the activity and activation of mild rheumatoid arthritis—a pilot study. Scand J Rheumatol 32(4):211–215
35. Jafarnejad S, Djafarian K, Fazeli MR, Yekaninejad MS, Rostamian A, Keshavarz SA (2017) Effects of a multispecies probiotic supplement on bone health in osteopenic postmenopausal women: a randomized, double-blind, controlled trial. J Am Coll Nutr 36(7):497–506. https://doi.org/10.1080/07315724.2017.1318724
36. Jenks K, Stebbings S, Burton J, Schultz M, Herbison P, Highton J (2010) Probiotic therapy for the treatment of spondyloarthritis: a randomized controlled trial. J Rheumatol 37(10):2118–2125. https://doi.org/10.3899/jrheum.100193
37. Jones M, Martoni C, Prakash S (2012) Cholesterol lowering and inhibition of sterol absorption by *Lactobacillus reuteri* NCIMB 30242: a randomized controlled trial. Eur J Clin Nutr 66(11):1234
38. Kouchaki E, Tamtaji OR, Salami M, Bahmani F, Daneshvar Kakhaki R, Akbari E, Tajabadi-Ebrahimi M, Jafari P, Asemi Z (2017) Clinical and metabolic response to probiotic supplementation in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled trial. Clin Nutr 36(5):1245–1249. https://doi.org/10.1016/j.clnu.2016.08.015
39. Minami J, Kondo S, Yanagisawa N, Odamaki T, Xiao JZ, Abe F, Nakajima S, Hamamoto Y, Saitoh S, Shimoda T (2015) Oral administration of *Bifidobacterium breve* B-3 modifies metabolic functions in adults with obese tendencies in a randomised controlled trial. J Nutr Sci 4:e17. https://doi.org/10.1017/jns.2015.5
40. Mohseni S, Bayani M, Bahmani F, Tajabadi-Ebrahimi M, Bayani MA, Jafari P, Asemi Z (2017) The beneficial effects of probiotic administration on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind,

placebo-controlled trial. Diabetes Metab Res Rev. https://doi.org/10.1002/dmrr.2970
41. Nagata Y, Yoshida M, Kitazawa H, Araki E, Gomyo T (2010) Improvements in seasonal allergic disease with *Lactobacillus plantarum* no. 14. Biosci Biotechnol Biochem 74(9):1869–1877. https://doi.org/10.1271/bbb.100270
42. Natarajan R, Pechenyak B, Vyas U, Ranganathan P, Weinberg A, Liang P, Mallappallil MC, Norin AJ, Friedman EA, Saggi SJ (2014) Randomized controlled trial of strain-specific probiotic formulation (Renadyl) in dialysis patients. BioMed Res Int 2014:568571. https://doi.org/10.1155/2014/568571
43. Panahi Y, Ghanei M, Vahedi E, Mousavi SH, Imani S, Sahebkar A (2017) Efficacy of probiotic supplementation on quality of life and pulmonary symptoms due to sulfur mustard exposure: a randomized double-blind placebo-controlled trial. Drug Chem Toxicol 40(1):24–29. https://doi.org/10.3109/01480545.2016.1166250
44. Pinto-Sanchez MI, Hall GB, Ghajar K, Nardelli A, Bolino C, Lau JT, Martin FP, Cominetti O, Welsh C, Rieder A, Traynor J, Gregory C, De Palma G, Pigrau M, Ford AC, Macri J, Berger B, Bergonzelli G, Surette MG, Collins SM, Moayyedi P, Bercik P (2017) Probiotic *Bifidobacterium longum* NCC3001 reduces depression scores and alters brain activity: a pilot study in patients with irritable bowel syndrome. Gastroenterology 153(2):448–459 e448. https://doi.org/10.1053/j.gastro.2017.05.003
45. Rajkumar H, Mahmood N, Kumar M, Varikuti SR, Challa HR, Myakala SP (2014) Effect of probiotic (VSL#3) and omega-3 on lipid profile, insulin sensitivity, inflammatory markers, and gut colonization in overweight adults: a randomized, controlled trial. Mediat Inflamm 2014:348959. https://doi.org/10.1155/2014/348959
46. Redondo N, Nova E, Gheorghe A, Díaz LE, Hernández A, Marcos A (2017) Evaluation of *Lactobacillus coryniformis* CECT5711 strain as a coadjuvant in a vaccination process: a randomised clinical trial in healthy adults. Nutr Metab 14(1):2
47. Sepideh A, Karim P, Hossein A, Leila R, Hamdollah M, Mohammad EG, Mojtaba S, Mohammad S, Ghader G, Seyed Moayed A (2015) Effects of multistrain probiotic supplementation on glycemic and inflammatory indices in patients with nonalcoholic fatty liver disease: a double-blind randomized clinical trial. J Am Coll Nutr. https://doi.org/10.1080/07315724.2015.1031355
48. Shariaty Z, Mahmoodi Shan GR, Farajollahi M, Amerian M, Behnam Pour N (2017) The effects of probiotic supplement on hemoglobin in chronic renal failure patients under hemodialysis: a randomized clinical trial. J Res Med Sci 22:74. https://doi.org/10.4103/jrms.JRMS_614_16
49. Sharma B, Srivastava S, Singh N, Sachdev V, Kapur S, Saraya A (2011) Role of probiotics on gut permeability and endotoxemia in patients with acute pancreatitis: a double-blind randomized controlled trial. J Clin Gastroenterol 45(5):442–448. https://doi.org/10.1097/MCG.0b013e318201f9e2
50. Shoaei T, Heidari-Beni M, Tehrani HG, Feizi A, Esmaillzadeh A, Askari G (2015) Effects of probiotic supplementation on pancreatic beta-cell function and C-reactive protein in women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial. Int J Prev Med 6:27. https://doi.org/10.4103/2008-7802.153866
51. Sierra S, Lara-Villoslada F, Sempere L, Olivares M, Boza J, Xaus J (2010) Intestinal and immunological effects of daily oral administration of *Lactobacillus salivarius* CECT5713 to healthy adults. Anaerobe 16(3):195–200
52. Soleimani A, Zarrati Mojarrad M, Bahmani F, Taghizadeh M, Ramezani M, Tajabadi-Ebrahimi M, Jafari P, Esmaillzadeh A, Asemi Z (2017) Probiotic supplementation in diabetic hemodialysis patients has beneficial metabolic effects. Kidney Int 91(2):435–442. https://doi.org/10.1016/j.kint.2016.09.040
53. Vaghef-Mehrabany E, Alipour B, Homayouni-Rad A, Sharif SK, Asghari-Jafarabadi M, Zavvari S (2014) Probiotic supplementation improves inflammatory status in patients with rheumatoid arthritis. Nutrition 30(4):430–435. https://doi.org/10.1016/j.nut.2013.09.007
54. Villar-Garcia J, Guerri-Fernandez R, Moya A, Gonzalez A, Hernandez JJ, Lerma E, Guelar A, Sorli L, Horcajada JP, Artacho A, G Knobel DA H (2017) Impact of probiotic *Saccharomyces boulardii* on the gut microbiome composition in HIV-treated patients: a double-blind, randomised, placebo-controlled trial. PLoS One 12(4):e0173802. https://doi.org/10.1371/journal.pone.0173802
55. Wang I-K, Wu Y-Y, Yang Y-F, Ting I-W, Lin C-C, Yen T-H, Chen J-H, Wang C-H, Huang C-C, Lin H-C (2015) The effect of probiotics on serum levels of cytokine and endotoxin in peritoneal dialysis patients: a randomised, double-blind, placebo-controlled trial. Benef Microbes 6(4):423–430
56. Xiao J (2006) Effect of probiotic *Bifidobacterium longum* BBS36 in relieving clinical symptoms and modulating plasma cytokine levels of Japanese cedar pollinosis during the pollen season. A randomized double-blind, placebocontrolled trial. J Investig Allergol Clin Immunol 16:86–93
57. Yamamoto K, Yokoyama K, Matsukawa T, Kato S, Kato S, Yamada K, Hirota T (2016) Efficacy of prolonged ingestion of *Lactobacillus acidophilus* L-92 in adult patients with atopic dermatitis. J Dairy Sci 99(7):5039–5046
58. Zamani B, Golkar HR, Farshbaf S, Emadi-Baygi M, Tajabadi-Ebrahimi M, Jafari P, Akhavan R, Taghizadeh M, Memarzadeh MR, Asemi Z (2016) Clinical and metabolic response to probiotic supplementation in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. Int J Rheum Dis. https://doi.org/10.1111/1756-185x.12888
59. Mazidi M, Rezaie P, Ferns GA, Vatanparast H (2017) Impact of probiotic administration on serum C-reactive protein concentrations: systematic review and meta-analysis of randomized control trials. Nutrients 9(1):20
60. Ma Y-Y, Li L, Yu C-H, Shen Z, Chen L-H, Li Y-M (2013) Effects of probiotics on nonalcoholic fatty liver disease: a meta-analysis. World J Gastroenterol 19(40):6911
61. Liu D, Jiang X-Y, Zhou L-S, Song J-H, Zhang X (2016) Effects of probiotics on intestinal mucosa barrier in patients with colorectal cancer after operation: meta-analysis of randomized controlled trials. Medicine 95(15):e3342
62. Aqaeinezhad Rudbane SM, Rahmdel S, Abdollahzadeh SM, Zare M, Bazrafshan A, Mazloomi SM (2018) The efficacy of probiotic supplementation in rheumatoid arthritis: a meta-analysis of randomized, controlled trials. Inflammopharmacology 26:67–76
63. Tam CS, Redman LM (2013) Adipose tissue inflammation and metabolic dysfunction: a clinical perspective. Horm Mol Biol Clin Investig 15(1):19–24
64. Morita H, He F, Fuse T, Ouwehand AC, Hashimoto H, Hosoda M, Mizumachi K, Kurisaki J (2002) Adhesion of lactic acid bacteria to caco-2 cells and their effect on cytokine secretion. Microbiol Immunol 46(4):293–297
65. He F, Ouwehand AC, Isolauri E, Hashimoto H, Benno Y, Salminen S (2001) Comparison of mucosal adhesion and species identification of bifidobacteria isolated from healthy and allergic infants. Pathog Dis 30(1):43–47
66. Pankevich E, Astakhova A, Chistyakov D, Sergeeva M (2017) Antiinflammatory effect of rosiglitazone via modulation of mRNA stability of interleukin 10 and cyclooxygenase 2 in astrocytes. Biochemistry 82(11):1276–1284
67. Calcinaro F, Dionisi S, Marinaro M, Candeloro P, Bonato V, Marzotti S, Corneli R, Ferretti E, Gulino A, Grasso F (2005) Oral probiotic administration induces interleukin-10 production and prevents spontaneous autoimmune diabetes in the non-obese diabetic mouse. Diabetologia 48(8):1565–1575

68. Kaji R, Kiyoshima-Shibata J, Tsujibe S, Nanno M, Shida K (2018) Probiotic induction of interleukin-10 and interleukin-12 production by macrophages is modulated by co-stimulation with microbial components. J Dairy Sci 101(4):2838–2841
69. Icaza-Chávez M (2013) Gut microbiota in health and disease. Revista de Gastroenterología de México 78(4):240–248 **(English edition)**
70. Shacklett BL, Cox CA, Sandberg JK, Stollman NH, Jacobson MA, Nixon DF (2003) Trafficking of human immunodeficiency virus type 1-specific CD8+ T cells to gut-associated lymphoid tissue during chronic infection. J Virol 77(10):5621–5631
71. Malin M, Verronen P, Korhonen H, Syväoja E-L, Salminen S, Mykkänen H, Arvilommi H, Eerola E, Isolauri E (1997) Dietary therapy with Lactobacillus GG, bovine colostrum or bovine immune colostrum in patients with juvenile chronic arthritis: evaluation of effect on gut defence mechanisms. Inflammopharmacology 5(3):219–236
72. Vitaliti G, Pavone P, Guglielmo F, Spataro G, Falsaperla R (2014) The immunomodulatory effect of probiotics beyond atopy: an update. J Asthma 51(3):320–332
73. Rautava S, Kalliomäki M, Isolauri E (2005) New therapeutic strategy for combating the increasing burden of allergic disease: probiotics—a Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota (NAMI) Research Group report. J Allergy Clin Immunol 116(1):31–37