**Supplementary Table 1.** Search strategies used for online databases

The following databases were searched:

* PubMed
* Scopus
* Web of Science
* Cochrane Library

The search strategy was to combine searches of:

|  |  |
| --- | --- |
| Probiotic |  (Probiotics) OR (probiotic\*) OR ("cultured milk products") OR (yogurt) OR ("milk product") OR (kefir) OR (“dairy product”) OR (Bifidobacterium) OR (Bifido\*) OR (Bacteroides) OR (Bacteroid\*) OR (Lactobacillus) OR (Lactobacil\*) OR (Lactobacillaceae) OR (Pediococcus) OR (“Fermented Foods and Beverages”) OR (“Fermented milk”) OR (Nissle) OR (“Fermented Foods”) OR (Streptococ\*) OR (Saccharomyces) OR (Saccharomy) OR (Enterococcus) OR (Lactobacillales) OR (“Lactic acid bacteria”) OR (“Bacillus mesentericus”) OR (“Escherichia coli”) OR (acidophilus) OR (microorganism∗) OR (buttermilk) OR (lassi) OR (doogh) OR (dough) OR (dahi) OR (amasi) OR (filmjolk) OR (chal) OR (VSL#3) OR (Synbiotic\*) OR (Symbiotic\*) |
| Population  | (Diabetes) OR (“Diabetes Mellitus”) OR (hyperglycemia) OR (diabet\*) |
| Study design |  Randomized OR random OR "Random allocation" OR "Random assignment" OR Intervention OR "Clinical trial" OR "Randomized controlled trial" OR trial OR Placebo OR "Double-blind" OR "Single-blind" OR "Random Allocation" OR "Randomised clinical trial")  |

 “Probiotic, “population”, and “study design” related terms

**Supplementary Table 2**. References for excluded studies

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| --- |
| **Wrong population (n=4)**1**-**Mazloomi M, Tanideh N, Rezainzadeh A. The effects soymilk fremented with bifidobacterium lactis and containing omega-3 on haematological, oxidative stress, anti-oxidant and inflammatory parameters in type 2 diabetic rats. Iranian Journal of Diabetes and Metabolism. 2015;14(6):379-89.2- Kushugulova A, Benberin V, Karabayeva R, Saduakhasova S, Kozhakhmetov S, Shakhabayeva G, et al. Randomized Clinical Trial: Efficacy of a New Synbiotic in Adults with Metabolic Syndrome. Cent Asian J Glob Health. 2013;2(Suppl)3- Parastouei K, Saeidipoor S, Sepandi M, Abbaszadeh S, Taghdir M. Effects of synbiotic supplementation on the components of metabolic syndrome in military personnel: a double-blind randomised controlled trial. BMJ Mil Health.4- Simon MC, Strassburger K, Nowotny B, Kolb H, Nowotny P, Burkart V, et al. Intake of Lactobacillus reuteri improves incretin and insulin secretion in glucose-tolerant humans: a proof of concept. Diabetes Care. 2015;38(10):1827-34. |
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| **First author, year**  | **Sequence generation** | **Allocation concealment** | **Blinding of participants** | **Blinding of outcome assessment** | **Incomplete outcome data** | **Selective reporting** | **Funding** | **Overall**  |
| Abbasi, 2017 | U | U | L | L | L | L | L | Fair |
| Abbasi, 2018 | L | L | L | L | L | L | L | Good  |
| Arani, 2018 | L | L | L | L | L | L | L | Good |
| Asemi, 2013 | L | L | L | L | L | L | L | Good |
| Asemi, 2014 | L | L | L | L | L | L | L | Good |
| Asemi, 2015 | L | L | L | L | L | L | L | Good |
| Asemi, 2017 | L | L | L | L | L | L | L | Good |
| Bahmani, 2015 | L | L | L | L | L | L | L | Good |
| Ebrahimi, 2017 | L | L | L | L | L | L | L | Good |
| Firouzi, 2015 | L | L | L | L | L | L | L | Good |
| Kobyliak, 2018 | L | L | L | L | L | L | L | Good |
| Mafi, 2018 | L | L | L | L | L | L | L | Good |
| Miraghajani, 2017 | L | L | L | L | L | L | L | Good |
| Mobini, 2017 | U | U | L | L | L | L | L | Fair |
| Soleimani, 2017 | L | L | L | L | L | L | L | Good |

**Supplementary Table 3**. Study quality and risk of bias assessment using the Cochrane Collaboration’s tool

**Supplementary Table 4**. GRADE assessment of confidence in estimates of effect in randomized trials

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **Participants (studies)** | **Risk of bias1** | **Inconsistency2** | **Indirectness3** | **Imprecision4** | **Publication bias5** | **Certainty of evidence6** |
| ALP (U/L) | 310 (4) | Not Serious7 | Serious8 (I2=63.3) | Serious9 | Serious10 | NA11 | Very Low12 |
| ALT (U/L) | 397 (6) | Not Serious13 | Serious14 (I2=58.1) | Serious15 | Serious16 | NA17 | Very Low18 |
| AST (U/L) | 397 (6) | Not Serious19 | Not Serious(I2=43.7) | Serious20 | Serious21 | NA22 | Low23 |
| Bilirubin (mg/dl) | 256 (3) | Not Serious24 | Serious25 (I2=93.1) | Serious26 | Serious27 | NA28 | Very Low29 |
| BUN (mg/dl) | 386 (5) | Not Serious30 | Not Serious(I2=36.1) | Serious31 | Serious32 | NA33 | Low34 |
| [Creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0) (mg/dl) | 426 (6) | Not Serious35 | Serious36 (I2=87.7) | Serious37 | Serious38 | NA39 | Very Low40 |
| GFR (mL/min/1.73m2) | 236 (3) | Not Serious41 | Serious42 (I2=90.7) | Serious43 | Serious44 | NA45 | Very Low46 |
| Microalbuminuria (Alb/Cr (mg/gr) | 139 (3) | Serious47 | Serious48 (I2=80.9) | Not Serious | Serious49 | NA50 | Very Low51 |
| [Alkaline Phosphatase;](https://labtestsonline.org/tests/alkaline-phosphatase-alp) [Alanine Aminotransferase;](https://labtestsonline.org/tests/alanine-aminotransferase-alt) [Aspartate Aminotransferase; Blood urea nitrogen; Glomerular filtration rate](https://labtestsonline.org/tests/aspartate-aminotransferase-ast) |

1. Cochrane tool was used to assess trial quality across the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Trials were considered good quality if all domains were low RoB; low quality if more than one domain was high RoB, and unclear quality if two or more domains were unclear RoB. We downgraded one level (Serious) if 50% to 75% of RCTs were at high RoB and two levels (very serious) if more than 75% of RCTs were high ROB
2. We downgraded one level for inconsistency when I2 ≥50%. Where I2>50%, and the sensitivity analysis did not explain the source of heterogeneity. The I2 was ≤ 50% inconsistency considered as Not serious limitation.
3. We downgraded one level for indirectness if more than 50% included trials have been conducted in the same geographical location.
4. We downgraded one level for imprecision if the number of participants was less than 400. We also downgraded one level if point estimate was smaller than 5% baseline value (6.9 U/L for ALT, 4.6 U/L for AST, 25.87 U/l for ALP, 4.82 mg/dl for BUN, 0.5 mg/dl for bilirubin and [creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0), 0.5 mL/min/1.73m2 for GFR, and 0.5 (Alb/Cr (mg/gr)) for microalbuminuria, or point estimate surpassed smaller than 5% baseline value, but 95%CI overlapped with it.
5. We assessed for potential publication bias when ≥10 trials were available. We downgraded if there was evidence of bias with Egger's test (P<0.05) or there was evidence of asymmetry in the funnel plot.
6. Data from RCTs begin with a grade of “HIGH”. Downgraded for high RoB, inconsistency, indirectness, imprecision and Publication bias.
7. Less than 50% of trials (1 of 4) were at low quality. Not downgraded.
8. I2=63.3, P heterogeneity=0.043. The sensitivity analysis did not explain the source of heterogeneity. Downgraded.
9. Approximately more than half of trials (3 of 4) were conducted in Iran that limited the generalizability of the findings. Downgraded.
10. The number of participants was less than <400. Downgraded.
11. Publication bias test was not assessed because n<10.
12. Data from RCTs begin with a grade of “HIGH”. Downgraded for inconsistency, indirectness and imprecision.
13. Less than 50% of trials (2 of 6) were at low quality. Not downgraded.
14. I2=58.1, P heterogeneity=0.036. The sensitivity analysis did not explain the source of heterogeneity. Downgraded.
15. Approximately the half of trials (3 of 6) were conducted in Iran that limited the generalizability of the findings. Downgraded.
16. The number of participants was less than <400. Downgraded.
17. Publication bias test was not assessed because n<10.
18. Data from RCTs begin with a grade of “HIGH”. Downgraded for inconsistency, indirectness and imprecision.
19. Less than 50% of trials (2 of 6) were at low quality. Not downgraded.
20. Approximately the half of trials (3 of 6) were conducted in Iran that limited the generalizability of the findings. Downgraded.
21. The number of participants was less than <400. Downgraded.
22. Publication bias test was not assessed because n<10.
23. Data from RCTs begin with a grade of “HIGH”. Downgraded for indirectness and imprecision.
24. Less than 50% of trials (1 of 3) were at low quality. Not downgraded.
25. I2=93.1, P heterogeneity<0.001. The sensitivity analysis did not explain the source of heterogeneity. Downgraded.
26. Approximately more than half of trials (2 of 3) were conducted in Iran that limited the generalizability of the findings. Downgraded.
27. The number of participants was less than <400. Downgraded.
28. Publication bias test was not assessed because n<10.
29. Data from RCTs begin with a grade of “HIGH”. Downgraded for inconsistency, indirectness and imprecision.
30. All of included trials were at high quality. Not downgraded.
31. Approximately more than half of trials (4 of 5) were conducted in Iran that limited the generalizability of the findings. Downgraded.
32. The number of participants was less than <400. Downgraded.
33. Publication bias test was not assessed because n<10.
34. Data from RCTs begin with a grade of “HIGH”. Downgraded for indirectness and imprecision.
35. Less than 50% of trials (2 of 6) were at low quality. Not downgraded.
36. I2=87.7, P heterogeneity<0.001. The sensitivity analysis did not explain the source of heterogeneity. Downgraded.
37. The most of trials (5 of 6) were conducted in Iran that limited the generalizability of the findings. Downgraded.
38. More than 400 participants were available. The point estimate was smaller than 5% baseline weight (WMD= -0.10 mg/dl). Downgraded.
39. Publication bias test was not assessed because n<10.
40. Data from RCTs begin with a grade of “HIGH”. Downgraded for inconsistency, indirectness and imprecision.
41. Less than 50% of trials (1 of 3) were at low quality. Not downgraded.
42. I2=90.7, P heterogeneity<0.001. The sensitivity analysis did not explain the source of heterogeneity. Downgraded.
43. The most of trials (2 of 3) were conducted in Iran that limited the generalizability of the findings. Downgraded.
44. The number of participants was less than <400. Downgraded.
45. Publication bias test was not assessed because n<10.
46. Data from RCTs begin with a grade of “HIGH”. Downgraded for inconsistency, indirectness and imprecision.
47. Approximately more than half of trials (2 of 3) were at low quality. Main trial limitation was lack of random sequence generation, allocation concealment. Downgraded.
48. I2=80.9, P heterogeneity=0.005. The sensitivity analysis did not explain the source of heterogeneity. Downgraded.
49. The number of participants was less than <400. Downgraded.
50. Publication bias test was not assessed because n<10.
51. Data from RCTs begin with a grade of “HIGH”. Downgraded for ROB, inconsistency and imprecision.

**Supplementary Table 5.** Meta-analysis showing the effect of probiotics/synbiotics supplementation on liver and renal biomarkers (all analyses were conducted using random effects model)

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Participants (Studies)** | **Meta- analysis** | **Heterogeneity** |
| WMD (95% CI) | *P* effect | Q statistic | P within group | I2 % |
| **Liver biomarkers** |
| ALP (U/L) | 310 (4) | 7.26 (-3.39, 17.91) | 0.182 | 8.17 | 0.043 | 63.3 |
| ALT (U/L) | 397 (6) | -0.76 (-4.12, 2.58) | 0.653 | 11.82 | 0.037 | 57.7 |
| AST (U/L) | 397 (6) | -0.91 (-3.05, 1.22) | 0.40 | 6.95 | 0.224 | 28.1 |
| Bilirubin (mg/dl) | 256 (3) | -0.04 (-0.16, 0.08) | 0.529 | 14.45 | 0.001 | 86.2 |
| **Renal biomarkers** |
| BUN (mg/dl) | 386 (5) | -0.87 (-1.91, 0.18) | 0.104 | 6.29 | 0.180 | 36.1 |
| [Creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0) (mg/dl) | 426 (6) | -0.10 (-0.20, -0.00) | 0.010 | 40.61 | <0.001 | 87.7 |
| GFR (mL/min/1.73m2) | 236 (3) | 4.55 (-0.94, 10.05) | 0.104 | 21.42 | <0.001 | 90.7 |
| Microalbuminuria (Alb/Cr (mg/gr)) | 139 (3) | -10.36 (-22.87, 2.16) | 0.105 | 10.46 | 0.005 | 80.9 |
| ALP, [Alkaline Phosphatase; ALT,](https://labtestsonline.org/tests/alkaline-phosphatase-alp) [Alanine Aminotransferase; AST,](https://labtestsonline.org/tests/alanine-aminotransferase-alt) [Aspartate Aminotransferase; BUN, Blood urea nitrogen; GFR, Glomerular filtration rate](https://labtestsonline.org/tests/aspartate-aminotransferase-ast) |

**Supplementary Table 6.** Meta-analysis showing the effect of probiotics/synbiotics supplementation on liver and renal biomarkers across subgroups (all analyses were conducted using random effects model)

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Participants (Studies)** | **Meta- analysis** | **Heterogeneity** |
| WMD (95% CI) | *P* effect | Q statistic | P within group | I2 % |
| **Duration of the intervention (week)** |
| ***Less than 12 weeks*** |
| ALP (U/L) | 310 (4) | 7.441 (-2.870, 17.752) | 0.15 | 7.75 | 0.05 | 62.4 |
| ALT (U/L) | 368 (5) | -0.875 (-4.568, 2.819)  | 0.64 | 11.35 | 0.02 | 64.7 |
| AST (U/L) | 368 (5) |  0.186 (-2.585, 2.957)  | 0.89 | 8.11 | 0.08 | 50.7 |
| Bilirubin (mg/dl) | 256 (3) | -0.041 (-0.168, 0.086)  | 0.53 | 14.6 | 0.001 | 86.3 |
| BUN (mg/dl) | 206 (2) | -0.374 (-1.466, 0.718)  | 0.5 | 1.7 | 0.19 | 41.3 |
| Creatinine (mg/dl) | 246 (3) | -0.028 (-0.125, 0.069) | 0.57 | 23.38 | <0.001 | 91.4 |
| ***12 weeks and more*** |
| ALP (U/L) | 136 (1) | 0.640 (-5.045, 6.325) | 0.82 | 0.0 | - | - |
| ALT (U/L) | 165 (2) | -0.756 (-4.922, 3.410)  | 0.72 | 0.59 | 0.44 | 0.0 |
| AST (U/L) | 165 (2) | -0.440 (-5.398, 4.518) | 0.86 | 2.53 | 0.11 | 60.5 |
| Bilirubin (mg/dl) | 136 (1) | 0.030 (-0.023, 0.083)  | 0.26 | 0.0 | - | - |
| BUN (mg/dl) | 316 (4) | -1.215 (-1.933, -0.496) | 0.001 | 2.88 | 0.41 | 0.0 |
| Creatinine (mg/dl) | 316 (4) | -0.168 (-0.397, 0.062)  | 0.15 | 23.21 | <0.001 | 87.1 |
| **Renal complications** |  |  |  |  |  |  |
| ***Yes***  |  |  |  |  |  |  |
| BUN (mg/dl) | 180 (3) | -1.634 (-4.040, 0.771)  | 0.18 | 2.87 | 0.23 | 30.4 |
| [Creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0) (mg/dl) | 220 (4) | -0.209 (-0.322, -0.096)  | <0.001 | 5.6 | 0.13 | 46.7 |
| ***No***  |  |  |  |  |  |  |
| BUN (mg/dl) | 206 (2) | -0.540 (-2.120, 1.040)  | 0.5 | 3.21 | 0.07 | 68.9 |
| [Creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0) (mg/dl) | 206 (2) | 0.014 (-0.017, 0.046)  | 0.36 | 0.1 | 0.75 | 0.0 |
| ALP, [Alkaline Phosphatase; ALT,](https://labtestsonline.org/tests/alkaline-phosphatase-alp) [Alanine Aminotransferase; AST,](https://labtestsonline.org/tests/alanine-aminotransferase-alt) [Aspartate Aminotransferase; BUN, Blood urea nitrogen](https://labtestsonline.org/tests/aspartate-aminotransferase-ast) |

**Supplementary Table 7**. Sensitivity analysis showing the effect of probiotics/synbiotics supplementation on liver and renal biomarkers in patients with diabetes (all analyses were conducted using random effects model)

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Participants (Studies)** | **Meta- analysis** | **Heterogeneity** |
| WMD (95% CI) | *P* effect | Q statistic | P within group | I2 % |
| **Excluding studies supplemented synbiotic** |
| ALP (U/L)1 | 248 (3) | 1.35 (3.94, 6.64) | 0.61 | 1.61 | 0.44 | 0.0 |
| ALT (U/L)1 | 335 (5) | -2.003 (-4.61, 0.6) | 0.13 | 4.81 | 0.3 | 16.9 |
| AST (U/L)1 | 335 (5) | 1.13 (-2.48, 4.74) | 0.54 | 8.82 | 0.06 | 54.6 |
| BUN (mg/dl)2 | 316 (4) | -1.21 (-1.93, -0.49) | 0.001 | 2.88 | 0.41 | 0.0 |
| [Creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0) (mg/dl)2 | 356 (5) | -0.15 (-0.28, -0.015) | 0.03 | 32.99 | <0.001 | 87.9 |
| **Excluding studies recruited mix population of type 1 and type diabetic patients** |
| BUN (mg/dl)3 | 266 (3) | -0.65 (-1.62, 0.32) | 0.18 | 3.29 | 0.19 | 39.3 |
| [Creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0) (mg/dl)3 | 306 (4) | -0.05 (-0.14, 0.03) | 0.25 | 23.44 | <0.001 | 87.2 |
| **Excluding studies recruited diabetic patients with liver complications** |
| ALT (U/L)4 | 339 (5) | -0.911 (-5.232, 3.410)  | 0.67 | 11.75 | 0.01 | 0.66 |
| AST (U/L)4 | 339 (5) | -0.440 (-2.660, 1.781) | 0.69 | 5.39 | 0.25 | 25.8 |
| ALP, [Alkaline Phosphatase; ALT,](https://labtestsonline.org/tests/alkaline-phosphatase-alp) [Alanine Aminotransferase; AST,](https://labtestsonline.org/tests/alanine-aminotransferase-alt) [Aspartate Aminotransferase; BUN, Blood urea nitrogen](https://labtestsonline.org/tests/aspartate-aminotransferase-ast) |

1. The studies by Bahmani etal and Asemi (2017) etal were excluded from analysis.
2. The study by Ebrahimi etal was excluded from analysis.
3. The studies by Soleimani etal and Mafi etal were excluded from analysis
4. The study by Kobyliak etal was excluded from analysis.