International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn24103

Influences of probiotics and gut microbiota on immunomodulation for the treatment of patients with cancer: a systematic review

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DOI: https://doi.org/10.54448/ijn24103
Received: 10-14-2023; Revised: 12-17-2023; Accepted: 12-22-2023; Published: 01-09-2024; IJN-id: e24103

Abstract

Introduction: Immunomodulation and immunostimulation are the main mechanisms of action of probiotics in the fight against cancer. **Objective:** It was to carry out a systematic review of the influences of probiotics and gut microbiota on immunomodulation for the treatment of cancer patients. **Methods:** The PRISMA Platform systematic review rules were followed. The research was carried out from September to October 2023 in the Web of Science, Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 125 articles were found, and 35 articles were evaluated in full and 18 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 45 studies with a high risk of bias and 15 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=55.4%>50%. It was concluded that probiotics suppress inflammation by inhibiting several signaling pathways and reducing the global activation of NF-κβ and the production of pro-inflammatory cytokines. Probiotics influence receptor antagonism, receptor expression, binding and expression of adapter proteins, expression of negative regulatory signal molecules, and mainly the induction of microRNAs. These microRNAs can modulate the gene expression of tumor cells together with regulatory T cells that have important functions in the tumor microenvironment, mainly in inducing immune evasion. Some modulatory effects of probiotics include the production of cytokines by epithelial cells, increased mucin secretion and phagocytosis and NK cell activity, activation of T and NKT cells, stimulation of IgA production, and decreased proliferation of T cells. The gut microbiota has a major impact on the systemic immune system. The specific microbiota controls cell differentiation in which CD4+ T cells (Th17 cells) secrete IL-17. The presence of Th17 cells and regulatory T cells is associated with the gut microbiota.

Keywords: Probiotics. Gut microbiota. Regulatory T cells. MicroRNAs. Cancer.

Introduction

In the gut microbiota setting, many epigenetic factors affect host microbial colonization. The gut

microbiota can affect the digestive system and immune system responses **[1]**. The microbiota mainly has a protective function and activates metabolic and trophic processes that protect the host from microbial pathogens through the production of bacteriocins, as well as competition for nutrients and binding to the microbiota **[2]**.

Furthermore, the gut microbiota is capable of fermenting non-digestible carbohydrates into short-chain fatty acids (SCFAs) and also plays a role in vitamin synthesis and iron absorption. Mucosa-associated lymphoid tissue is a very extensive tissue and complex part of the small intestine and colonic immune system organized in sites such as lymphoid follicles and Peyer's patches, in which lumenal antigens are received by antigen-presenting cells and stimulate the synthesis of immunoglobulin A (IgA) **[3]**.

Also, SCFAs also have a trophic effect, increasing the proliferation and cellular differentiation of gut epithelial cells. Furthermore, they are possible inhibitors of the proliferation of neoplastic cells. Bacteria in the gut lumen react to the immune system through pattern recognition receptors such as toll-like receptors (TLR) and recognize pathogens via PAMPs **[4]**.

In this context, immunomodulation and immunostimulation are the main mechanisms of action of probiotics, mainly related to the modulation of the gut microbiota, in addition to improving the barrier of the gut mucosa, preventing the passage of antigens into the bloodstream. Direct modulation of the immune system may be secondary to the induction of anti-inflammatory cytokines or by increased production of secretory IgA. The presence of immunoregulatory mechanisms (regulatory T cells – Treg -, interleukin 10 – IL-10, apoptosis, among others) helps in the control of pathological processes associated with excessive reactivity **[5]**.

Several bacterial species and their role as positive probiotic agents were evaluated, such as Lactobacillus and Bifidobacteria species. Thus, Lactobacillus, Bifidobacterium, and *Saccharomyces boulardii* are the bacteria and fungal species that participate as probiotics **[6-9]**.

Therefore, the present study aimed to carry out a systematic review of the influences of probiotics and gut microbiota on immunomodulation for the treatment of cancer patients.

Methods

Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 09/29/2023. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 09/29/2023.

Data Sources and Research Strategy

The literary search process was carried out from September to October 2023 and was developed based on Web of Science, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The descriptors (*MeSH Terms*) were used: *"Probiotics. Gut microbiota. Regulatory T cells. microRNAs. Cancer"*, and using the Boolean "and" between the MeSH terms and "or" between historical discoveries.

Study Quality and Risk of Bias

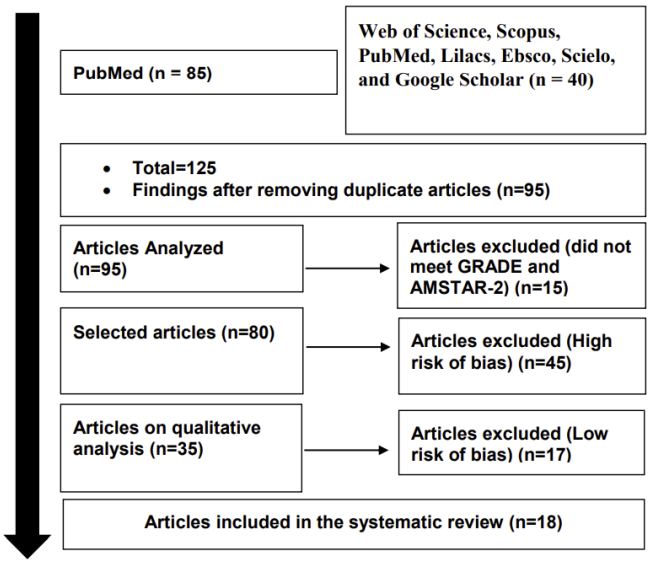
Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

Results and Discussion

Summary of Findings

A total of 125 articles were found that were subjected to eligibility analysis, with 18 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2=55.4%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 45 studies with a high risk of bias and 15 studies that did not meet GRADE and AMSTAR-2.

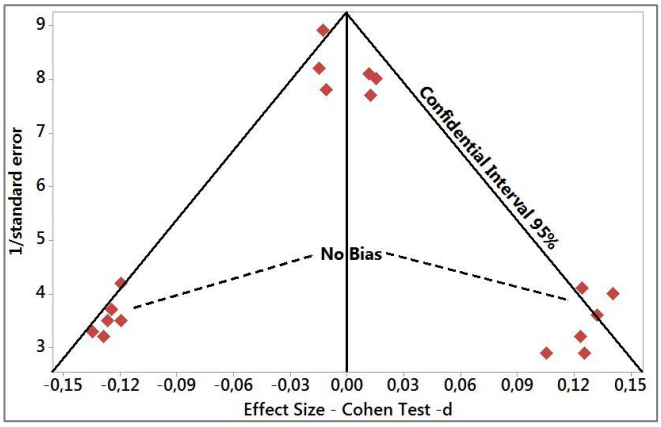
Figure 1. Selection of articles by exclusion based on GRADE and AMSTAR-2.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n= 18 studies).



Source: Own authorship.

Probiotics, Gut Microbiota and Cellular Physiology

The gut microbiota has an impact on cancer immune surveillance and immunotherapy. Although probiotics have traditionally been supplemented to promote treatments or sustain therapeutic benefits, the FDA has not approved any for use as immunotherapy. However, dietary fiber intake, prebiotic supplementation, and fecal microbiota transplantation have been found to increase the proportion of intratumoral CD8 + T cells and regulatory T cells (Tregs) **[10]**.

In this context, probiotics play a protective role against the colonization of gut pathogenic microbes and increase mucosal integrity by stimulating epithelial cells. Probiotics have innate capabilities in several ways, including receptor antagonism, receptor expression, binding and expression of adapter proteins, expression of negative regulatory signal molecules, induction of microRNAs, endotoxin tolerance, and ultimately secretion of immunomodulatory proteins. , lipids, and metabolites to modulate the immune system. Probiotic bacteria can affect homeostasis, inflammation, and immunopathology through direct or indirect effects on signaling pathways as immunosuppressants or activators **[11]**.

Furthermore, probiotics suppress inflammation by inhibiting several signaling pathways, such as the nuclear factor-κB (NF-κβ) pathway, possibly related to changes in mitogen-activated protein kinases and pattern recognition receptor pathways. Probiotics can also inhibit the binding of lipopolysaccharides to the CD14 receptor, thereby reducing overall NF-κβ activation and producing pro-inflammatory cytokines. Some effects of modulation by probiotics include the production of cytokines by epithelial cells, increased mucin secretion, increased phagocytosis activity and activation of T cells and natural killer T cells, stimulation of immunoglobulin A production, and decreased T cell proliferation. The specific microbiota controls the differentiation of cells in the gut lumen, in which Th17 cells secrete interleukin 17. The presence of Th17 cells and Tregs in the small intestine is associated with the gut microbiota, with preferential differentiation of Tregs and the absence of Th17 cells, possibly reflecting changes in the cytokines of the lumen itself and the gut microbiota **[12]**.

Added to this, recent discoveries suggest that the gut microbiota has an important impact on the systemic immune system. Th17 cells produce most pro-inflammatory cytokines such as IL-17, IL-21, and IL-22 and therefore play a notable

immunomodulatory role. The presence of Th17 cells in the small intestine is associated with gut microbiota, which allows for an increase in the number of regulatory cells Foxp3+ T cells (Treg). Both Th17 and Treg cells require TGF-β, while differentiation of Th17 cells also requires IL-6 **[3,4]**.

Main Clinical Studies – Probiotics, Tregs and Cancer

Regulatory T cells (Tregs) have important functions in the tumor microenvironment, mainly in inducing immune evasion. To find the underlying mechanism of Treg dysregulation in breast cancer tissues, a study by authors Moallemi-Rad et al. (2023) evaluated the expression of five long non-coding RNAs (lncRNAs) related to Tregs, namely FLICR (FOXP3 Regulating Long Intergenic Non-Coding RNA), NEST (IFNG-AS1), RMRP (RNA Component of RNA Processing Endoribonuclease mitochondrial), MAFTRR (MAF transcriptional regulatory RNA) and TH2-LCR (Th2 cytokine locus control region) in paired breast cancer and nearby non-cancerous tissues.

The expression levels of RMRP, TH2-LCR, MAFTRR, and GATA3-AS1 were significantly higher in breast cancer samples compared to non-tumor tissues. There were significant positive associations between the level of RMRP gene expression in tumor tissues and nuclear grade, tubule formation, and tumor size. Furthermore, there was a significant positive association between the expression levels of MAFTRR genes in tumor tissues and nuclear grade. Furthermore, FLICR expression levels were different between tumors with different HER2/neu receptor levels. Therefore, Treg-associated lncRNAs may contribute to the pathogenesis of breast cancer **[13]**.

The authors Huang et al. (2023) evaluated the use of probiotics in the postoperative period in the mitigation of gastrogut complications and gut microbiota disorders in patients with colorectal cancer (CRC) undergoing chemotherapy. We recruited 100 eligible patients with CRC who were treated with radical surgery and needed to receive chemotherapy. Half of them were randomly assigned to the Probio group to take a combination of probiotics from postoperative until the end of the first chemotherapy cycle. The other half of the patients who took a placebo were classified as the Placebo group. Fecal samples were collected preoperatively and after the first cycle of postoperative chemotherapy for high-throughput 16S rRNA sequencing and short-chain fatty acid (SCFA) analysis. The results showed that the administration of probiotics can effectively reduce chemotherapy-induced gastrogut complications, particularly diarrhea ($p<0.01$). Furthermore, chemotherapy also reduced the bacterial diversity indexes of the gut microbiota in CRC patients, which could be significantly increased with the use of probiotics. Furthermore, chemotherapy caused significant changes in the composition of the gut microbiota, as indicated by decreased levels of the Firmicutes phylum and increased Bacteroidetes, Proteobacteria, and Verrucomicrobia. In particular, several bacterial genera, such as Akkermansia and Clostridium, increased significantly, while Prevotella, Lactobacillus, and Roseburia decreased. However, administration of probiotics can restore these changes in taxa at both the phylum and genus levels and slightly increase genus levels of Bifidobacterium, Streptococcus, and Blautia. Furthermore, probiotics can also promote the production of SCFAs, particularly by increasing acetate, butyrate, and propionate **[14]**.

In this scenario, probiotics help maintain the defense of the gastrogut barrier, provide competitive adhesion to mucus and epithelial cells, and regulate gastrogut motility. A randomized, placebo-controlled clinical study for 15 days was carried out by authors Jiang et al. (2023) and investigated whether probiotics improve gastrogut health after craniotomy in patients with brain tumors. Participants were randomly divided into a probiotic group (4 g of probiotics twice a day) and a placebo group. A total of 200 participants were enrolled (probiotics: 100; placebo: 100). Time to first bowel movement and flatulence were significantly shorter in the probiotic group compared to the placebo group ($p<0.001$, respectively). Findings suggest that probiotics may improve gastrogut motility in patients undergoing craniotomy **[15]**.

A randomized, placebo-controlled clinical study was designed by authors Khazaei et al. (2023) evaluated the use of synbiotic supplementation (probiotics + prebiotics) as a safe and inexpensive adjuvant treatment to reduce common side effects of chemotherapy in women with breast cancer. A total of 67 women with a definitive diagnosis of breast cancer were hospitalized to receive one-day chemotherapy sessions and met the inclusion criteria. They received oral consumption of synbiotic supplements twice daily for 8 weeks. Eight weeks after the intervention and adjusting for confounders, the severity of chemotherapy complications, including abnormal defecation ($p=0.005$) and fatigue ($p<0/001$) significantly decreased in the synbiotic group compared with the placebo group. Furthermore, nausea/vomiting ($p=0.015$) and anorexia ($p<0.001$) decreased at the end of the study compared to the first visit but were not statistically significant compared to the placebo group **[16]**.

Added to this, a retrospective exploratory study developed by the authors Sugimoto et al. (2023) showed that synbiotics (*Lacticaseibacillus paracasei Shirota* strain, *Bifidobacterium breve Yakult* strain and galactooligosaccharides: LBG) help mitigate serious adverse events such as febrile neutropenia and diarrhea in esophageal cancer patients receiving neoadjuvant chemotherapy (NAC). Unfortunately, LBG therapy does not benefit all patients. This study was complementary

to a randomized controlled trial in which 81 patients with esophageal cancer were recruited and received prophylactic antibiotics or LBG combined with enteral nutrition (LBG+EN). The study included 73 of 81 patients from whom fecal samples were collected before and after NAC. Gut microbiota was analyzed using 16S rRNA gene sequencing and compared based on the degree of adverse events associated with NAC. Furthermore, the association between identified bacteria counts and adverse events and the mitigation effect of LBG+EN was also analyzed. The abundance of *Anaerostipes hadrus* and *Bifidobacterium pseudocatenulatum* in patients without febrile neutropenia or with only mild diarrhea was significantly higher ($p<0.05$) compared to those with febrile neutropenia or severe diarrhea. Furthermore, subgroup analyses of patients who received LBG+EN showed that *A. hadrus* fecal count before NAC was significantly associated with the risk of developing febrile neutropenia (OR, 0.11; 95% CI, 0.01-0 .60, P=0.019). Fecal *A. hadrus* count after NAC was positively correlated with gut concentrations of acetic acid (p=0.0007) and butyric acid (p=0.00005) **[17]**.

Finally, a clinical study carried out by authors Luke et al. (2023) enrolled participants with refractory advanced cancers to receive repeated intratumoral injections of SYNB1891, which is a modified live strain of the probiotic *Escherichia coli* Nissle 1917 (EcN) engineered to produce cyclic dinucleotides under hypoxia, leading to activation of the Stimulator of Interferon Genes (STING) on phagocytic antigen-presenting cells in tumors and activating innate immunity, alone or in combination with atezolizumab, with the main objective of evaluating the safety and tolerability of both regimens. A total of 24 participants received monotherapy in six cohorts and 8 participants received combination therapy in two cohorts. There were five cytokine release syndrome events with monotherapy, including one that met the criteria for doselimiting toxicity at the highest dose; no other SYNB1891-related serious adverse events occurred and no SYNB1891-related infections were observed. SYNB1891 was not detected in blood 6 or 24 hours after the first intratumoral dose or in tumor tissue 7 days after the first dose. Treatment with SYNB1891 resulted in activation of the STING pathway and target engagement, as assessed by upregulation of IFN-stimulated genes, chemokines/cytokines, and T-cell response genes in core biopsies obtained pre-dose and 7 days after the third dose. weekly dose. Furthermore, a dose-related increase in serum cytokines as well as stable disease was observed in 4 participants refractory to prior PD-1/L1 antibodies **[18]**.

Conclusion

It was concluded that probiotics suppress inflammation by inhibiting several signaling pathways and reducing the global activation of NF-κβ and the production of pro-inflammatory cytokines. Probiotics influence receptor antagonism, receptor expression, binding and expression of adapter proteins, expression of negative regulatory signal molecules, and mainly the induction of microRNAs. These microRNAs can modulate the gene expression of tumor cells together with regulatory T cells that have important functions in the tumor microenvironment, mainly in inducing immune evasion. Some modulatory effects of probiotics include the production of cytokines by epithelial cells, increased mucin secretion and phagocytosis and NK cell activity, activation of T and NKT cells, stimulation of IgA production, and decreased proliferation of T cells. The gut microbiota has a major impact on the systemic immune system. The specific microbiota controls cell differentiation, in which CD4+ T cells (Th17 cells) secrete IL-17. The presence of Th17 cells and regulatory T cells is associated with the gut microbiota.

Acknowledgement

Not applicable.

Ethical Approval

Not applicable.

Informed consent

Not applicable.

Funding

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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References

1. Legesse Bedada T, Feto TK, Awoke KS, Garedew AD, Yifat FT, Birri DJ. Probiotics for cancer alternative prevention and treatment. Biomed Pharmacother. 2020 Sep;129:110409. doi: 10.1016/j.biopha.2020.110409.
2. Thu MS, Ondee T, Nopsopon T, Farzana IAK, Fothergill JL, Hirankarn N, Campbell BJ, Pongpirul K. Effect of Probiotics in Breast Cancer: A Systematic Review and Meta-Analysis. Biology (Basel). 2023 Feb 9;12(2):280. doi: 10.3390/biology12020280.
3. Wang Z, Li L, Wang S, Wei J, Qu L, Pan L, Xu K. The role of the gut microbiota and probiotics associated with microbial metabolisms in cancer prevention and therapy. Front Pharmacol. 2022 Nov 14;13:1025860. doi: 10.3389/fphar.2022.1025860.
4. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. Nat Med. 2019 May;25(5):716-729. doi: 10.1038/s41591-019-0439-x.
5. Bieber K, Hundt JE, Yu X, Ehlers M, Petersen F, Karsten CM, Köhl J, Kridin K, Kalies K, Kasprick A, Goletz S, Humrich JY, Manz RA, Künstner A, Hammers CM, Akbarzadeh R, Busch H, Sadik CD, Lange T, Grasshoff H, Hackel AM, Erdmann J, König I, Raasch W, Becker M, Kerstein-Stähle A, Lamprecht P, Riemekasten G, Schmidt E, Ludwig RJ, 2023. Autoimmune pre-disease. Autoimmun Rev. Feb;22(2):103236. doi: 10.1016/j.autrev.2022.103236.
6. Green N, Miller T, Suskind D, Lee D. A Review of Dietary Therapy for IBD and a Vision for the Future. Nutrients. 2019, Apr 26;11(5). pii: E947. doi: 10.3390/nu11050947.
7. Chavele KM, Ehrenstein MR. Regulatory T-cells in systemic lupus erythematosus and rheumatoid arthritis. FEBS Lett; 2011, 585(23):3603-10.
8. Grant CR. Regulatory T-cells in autoimmune diseases: Challenges, controversies and—yet—unanswered questions; 2015, 14(2):105–16.
9. Liu H, Leung BP. CD4+CD25+ regulatory T cells in health and disease. Clin Exp Pharmacol Physiol; 2006, 33(5-6):519-24.
10. Singh A, Alexander SG, Martin S. Gut microbiome homeostasis and the future of probiotics in cancer immunotherapy. Front Immunol. 2023 May 16;14:1114499. doi: 10.3389/fimmu.2023.1114499.
11. Yousefi B, Eslami M, Ghasemian A, Kokhaei P, Salek Farrokhi A, Darabi N. Probiotics importance and their immunomodulatory properties. J Cell Physiol. 2019 Jun;234(6):8008-8018. doi: 10.1002/jcp.27559.
12. Yousefi B, Eslami M, Ghasemian A, Kokhaei P, Salek Farrokhi A, Darabi N. Probiotics importance and their immunomodulatory properties. J Cell Physiol. 2019 Jun;234(6):8008-8018. doi: 10.1002/jcp.27559.
13. Moallemi-Rad L, Ghorbani A, Dadyar M, Hussen BM, Rasul MF, Eslami S, Taheri M, Jamali E, Ghafouri-Fard S. Expression of Treg-associated lncRNAs in breast cancer. Pathol Res Pract. 2023 Jan; 241:154270. doi: 10.1016/j.prp.2022.154270.
14. Huang F, Li S, Chen W, Han Y, Yao Y, Yang L, Li Q, Xiao Q, Wei J, Liu Z, Chen T, Deng X. Postoperative Probiotics Administration Attenuates Gastrogut Complications and Gut Microbiota Dysbiosis Caused by Chemotherapy in Colorectal Cancer Patients. Nutrients. 2023 Jan 11;15(2):356. doi: 10.3390/nu15020356.
15. Jiang M, Zhang X, Zhang Y, Liu Y, Geng R, Liu H, Sun Y, Wang B. The Effects of Perioperative Probiotics on Postoperative Gastrogut Function in Patients with Brain Tumors: A Randomized, Placebo-Controlled Study. Nutr Cancer. 2023;75(4):1132-1142. doi: 10.1080/01635581.2023.2178929.
16. Khazaei Y, Basi A, Fernandez ML, Foudazi H, Bagherzadeh R, Shidfar F. The effects of synbiotics supplementation on reducing chemotherapy-induced side effects in women with breast cancer: a randomized placebo-controlled doubleblind clinical trial. BMC Complement Med Ther. 2023 Sep 26;23(1):339. doi: 10.1186/s12906-023-04165-8.
17. Sugimoto T, Atobe S, Kado Y, Takahashi A, Motoori M, Sugimura K, Miyata H, Yano M, Tanaka K, Doki Y, Shiraishi O, Yasuda T, Asahara T. Gut microbiota associated with the mitigation effect of synbiotics on adverse events of neoadjuvant chemotherapy in patients with esophageal cancer: A retrospective exploratory study. J Med Microbiol. 2023 Jun;72(6). doi: 10.1099/jmm.0.001723.
18. Luke JJ, Piha-Paul SA, Medina T, Verschraegen CF, Varterasian M, Brennan AM, Riese RJ, Sokolovska A, Strauss J, Hava DL, Janku F. Phase I Study of SYNB1891, an Engineered E. coli Nissle Strain Expressing STING Agonist, with and without Atezolizumab in Advanced Malignancies. Clin Cancer Res. 2023 Jul 5;29(13):2435-2444. doi: 10.1158/1078-0432.CCR-23-0118.