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THE IMPACT OF THE SUPPLEMENTATION OF PROBIOTICS USED AS PSYCHOBIOTICS ON ADOLESCENTS' AND YOUNG ADULTS' MENTAL HEALTH AND WELL-BEING AFFECTED BY THE COVID-19 PANDEMIC – A LITERATURE REVIEW OF THE CURRENT STATE OF KNOWLEDGE

S u m m a r y

Background. During the COVID-19 pandemic, various factors resulted in dramatic changes in the living environment of adolescents and young adults, consequently, harming their well-being and having a negative impact on their mental health. Therefore, supporting the mental health of young populations has been an imperative goal of recent research. There is a growing interest in the use of probiotics as psychobiotics to potentially aid in this goal. The review aimed to capture the current state of the literature on the impact of psychobiotic supplementation on mental health of adolescents and young adults in the light of the COVID-19 pandemic. The scope of the work included a systematic search of three databases: PubMed, Web of Science and Scopus, and the ClinicalTrials.gov clinical trial database.

Results and conclusion. A preliminary search did not allow to find studies referring to the COVID-19 pandemic. Narrowing queries down to studies conducted before the pandemic allowed to identify eighteen studies aimed at determining whether supplementation with probiotics improves the mental health of adolescents and young adults. In the included studies, the impact of probiotic consumption on stress levels, depressive symptoms, cognitive functioning and neurodevelopment were assessed most often. The evidence ambiguously indicates the effectiveness of probiotic interventions in ensuring mental health of adolescents and young adults. This is probably due to the limited number of small and short-term studies, as well as their heterogeneity. The results emerging from the existing literature are encouraging, but it is not possible to formulate an unequivocal recommendation. It is essential to plan and conduct new research into the role of probiotics in mental health and to verify their clinical efficacy in combating negative health effects caused by the coronavirus pandemic, including those affecting the mental health of adolescents and young adults.

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Introduction

Mental health has been threatened in an unprecedented manner by the COVID-19 pandemic. Indeed, the youngest population was most exposed to the negative effects of the COVID-19 pandemic in terms of mental health. A systematic review of data reporting the prevalence of major depressive disorder (n = 46) and anxiety disorders (n = 27) during the COVID-19 pandemic, conducted by The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), indicated that females were affected more by the pandemic than males, and younger age groups were more affected than older age groups [1]. The vulnerable developmental stage of children and adolescents may result in a higher risk of mental health problems, as do their fears of infection, home confinement, suspension of regular schoolwork and extracurricular activities, physical distancing mandates and larger-scale threats, such as global financial recessions and related consequences. Samji et al. [2] conducted a review of 16 articles presenting data on a total of 127,923 children and adolescents. Compared to pre-pandemic estimates, children and adolescents reported a higher prevalence of COVID-19-related fear and concerns, as well as depressive and anxious symptoms [2]. According to the studies included in the review, COVID-19 pandemic control measures had a detrimental effect on the mental health of children and adolescents [2]. It is worth pointing out that COVID-19 has been declared by UNESCO the most severe disruption to global education in history, estimating 1.6 billion students in over 190 countries were fully or partially out of school in 2020 [3]. As a result of school closures and broader social restrictions, young people were unable to gather in physical spaces, which surely affected their ability to learn, as well as their ability to interact with each other.

For this reason, due to numerous reports on the microbiome-gut-brain interaction, best illustrated in the animal models [4, 5, 6], the question is whether the modulation of the composition of the intestinal microbiota could reduce anxiety, fear and stress, and positively affect the mental health of adolescents and young adults, which worsened during the COVID-19 pandemic. The microbiota-gut-brain axis – bidirectional communication between the microbiome and the brain – has gained prominence as a potentially relevant pathway for maintaining human health. It has been also repeatedly highlighted by research in the past decade that gut microbiota influences brain function, cognition, and subsequent behavior in childhood and adolescence [7, 8]. It has been also demonstrated in animal models that gut microbiota is important for the initial development of the brain, including synaptogenesis and myelination of brain areas, as well as brain responsiveness and function throughout the lifespan [9, 10]. Additionally, it is known that the composition of the human microbiome in certain psychiatric and neurodevelopmental disorders differs from that in healthy individuals and is characterized by lower abundances of beneficial microbes (e.g. butyrate-producing *Faecalibacterium*) [11]. Such research has opened opportunities for the development and testing of a class of novel microbiome-targeted therapies including probiotics (and postbiotics), prebiotics and synbiotics reconfiguring the microbiome in a more beneficial manner, leading to improved brain function. The term "psychobiotics" refers to these therapies. Psychobiotics appear as a promising adjuvant for conditions such as depression, whose prevalence has been increasing since the COVID-19 pandemic, especially in the youth population. The advantages of psychobiotics include safety, low cost and lesser invasiveness than in some cases of traditional treatment of mental health issues and illnesseses [12]. There is still a great deal of nascent research in psychobiotics, but regrettably, it is still a long way to go before specific recommendations could be formulated. To date, there have been limited summaries examining the evidence that psychobiotics can improve cognitive and emotional functioning in both adolescents and young adults, as well as systematic reviews of the evidence in young people.

One class of psychobiotics – probiotics – is defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [13]. It is important that the strains of probiotic bacteria used for human consumption are not pathogenic and must survive the transit through the gastrointestinal tract [14]. Probiotics, depending on the bacterial strain, can release neuroactive substances [15]. According to research, the *Bifidobacterium* family is associated with the expression of GABA in the brain, whereas the *Enterococcus* and *Streptococcus* families are associated with serotonin production, and lactic acid bacteria are implicated in GABA and acetylcholine production [16]. *In vitro* and animal research has reliably laid out the psychotropic impacts of probiotics. For example, Bravo's et al. [17] findings highlighted the importance of bacteria in the bidirectional communication of the gut–brain axis. Supplementation of *L. rhamnosus* JB-1 reduced GABAAα2 mRNA expression in the prefrontal cortex and amygdala, but increased GABAAα2 in the hippocampus in mice model. Importantly, *L. rhamnosus* JB-1 also decreased the level of stress-induced corticosterone and anxiety and depression-related behavior. What is more significant, the neurochemical and behavioral impacts were not found in vagotomized mice, establishing the vagus nerve as a significant modulatory constitutive communication channel between the brain and the gut [17]. In another study [18], mice that received a mixture of four probiotic strains of lactic acid bacteria together with toxin lipopolysaccharide administration revealed a shorter duration of depression- and anxiety-like behavior and did not display as severe stress responses in adulthood compared to placebo [18]. Thus, there is an urgent need to translate these results to humans, where probiotics could prove to be a source of potential ingredients to support mental health in adolescents and young adults.

The aim of this review was to capture the current state of the literature on probiotics used as psychobiotics in healthy adolescents and young adults, to reduce anxiety stress and depression or improve emotional well-being and cognitive functioning that have deteriorated since the COVID-19 pandemic.

Materials and methods

Preliminary study

At the first stage, the ClinicalTrials.gov clinical trial database with PICO research questions [19] was searched to identify ongoing or completed studies that included: (P) a healthy young population, (I) an intervention with probiotic microorganisms, (C) comparing to placebo and/or treatment as the usual, (O) with endpoints that included measures of stress, anxiety, depression caused by the COVID-19 pandemic. No such studies were found. For this reason, it was decided to focus on searching the adequate and existing literature on this research topic and referring results to the COVID-19 pandemic.

Protocol

The same PICO scheme was used to fulfil the literature search. The search was performed on trials in healthy humans aged 11–25 for which active psychobiotic treatment included probiotics. The primary outcomes were anxiety and depression symptomatology and cognitive functions, and the secondary outcomes were stress and/or attention and/or neurodevelopment measures. In order to include all the possible studies, no restrictions were placed on the type, quantity or length of probiotic intervention, and studies using postbiotics/paraprobiotics and probiotic supplements in conjunction with other interventions (i.e. synbiotics) were also included. To that end, studies without a comparator, such as a placebo control group and/or treatment as the usual group, were also included.

Selection criteria

Controlled trials assessing anxiety/depression and/or stress, cognition, attention or neurodevelopment with at least one active treatment group in both subclinical and clinical populations were included. Inclusion criteria were as follows: (1) mean age in the range of 11–25 years old, (2) healthy and clinical samples, (3) minimal measures obtained pre- and postintervention, (4) probiotic administration in any form (alternatively: postbiotics, formerly paraprobiotics, and/or synbiotics) (5) anxiety/depression or cognition measured as primary or secondary outcomes with stress or attention, or neurodevelopment proxies also included when present, (6) the use of validated measurement instruments, (7) published and peer-reviewed data and (8) any date of publication. Exclusion criteria were as follows: (1) administration of prebiotics or other psychobiotics, (2) duplicate data/publications, and (3) unpublished data to ensure good research quality.

Search strategy, study selection, and data extraction

A search of the following three databases: Scopus, Web of Science, and PubMed was performed in March 2023 to identify formally published experimental trials on humans in the English language. Each database was searched using well-defined terms. The keywords utilized in the various databases can be made available upon request. The identified outputs were imported into Rayyan® web application, and duplicates were removed. A statistical synthesis of the results was not possible due to the heterogeneity of the study characteristics, including the characteristics of the population, the interventions and the outcomes. To guide the review process, the PRISMA diagram [20] was utilized.

Results

Study selection

The search strategy resulted in 226 de-duplicated studies that were screened to identify the thirteen eligible studies for inclusion. In addition, seven studies were identified by scanning bibliographies of included publications. The final output reached eighteen studies (Fig. 1).

Included studies characteristics

Table 1 provides a comprehensive summary of each study's characteristics [21-38]. All studies included healthy adolescents or young adults. Studies concerning clinical samples, including e.g. attention-deficit hyperactivity disorder (ADHD), learning disabilities and mood disorders, have been qualified in the exclusion criteria. Among the most common study designs, a cohort of selected university students was followed prior to, during, and after the exams [22-26, 28, 30, 38]. Various genera of microorganisms were utilized in the included studies: *Saccharomyces*, *Lacticaseibacillus*, *Lactiplantibacillus*, *Lactobacillus*, *Limosilactobacillus*, *Bifidobacterium*, and *Streptococcus*, which were administered singularly or as an appropriate combination thereof [29, 31, 36-38]. As capsules, powders or sachets, these were delivered with a daily dose of up to $1{\times}10^{11}$ colony-forming units (CFUs) and a length of intervention ranging from 14 days to approximately 2 years.

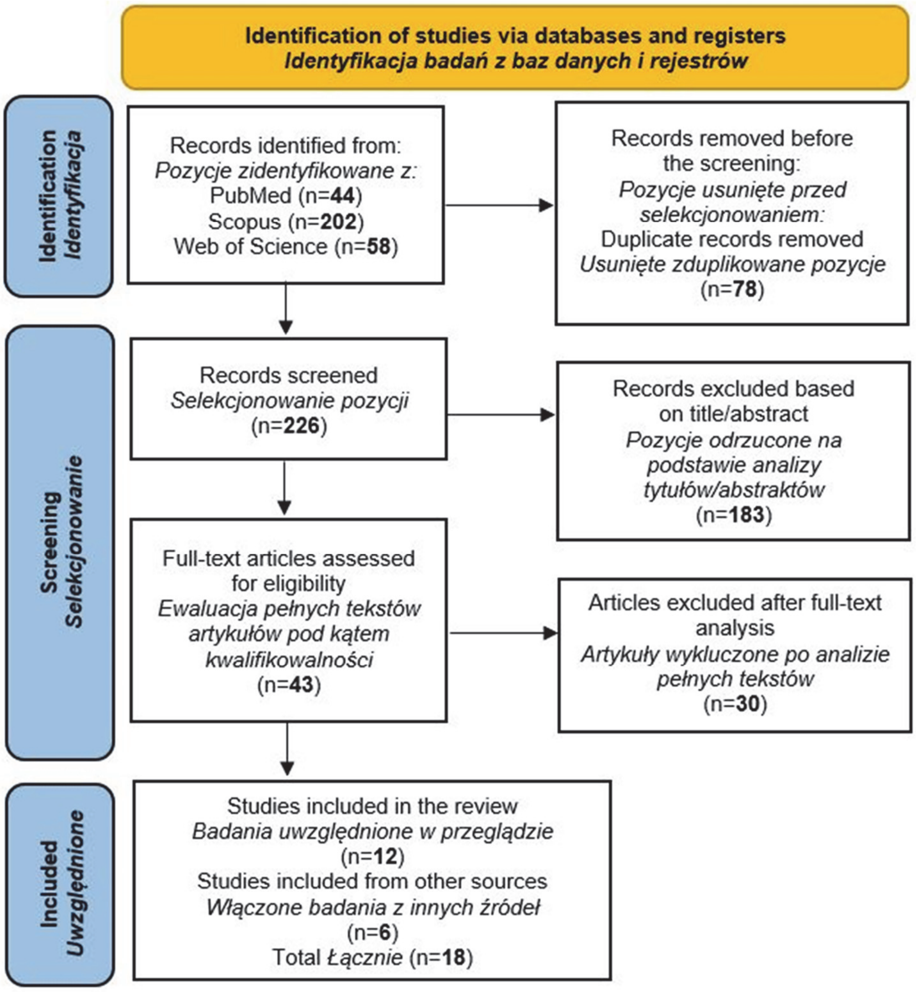

Fig. 1. PRISMA flowchart illustrating the identification of studies for inclusion
Rys. 1. Schemat blokowy PRISMA ilustrujący proces identyfikacji badań do włączenia

Heterogeneity

The outcomes of the study were highly heterogeneous. There were eight studies that included healthy participants under conditions of stress [22-24, 26- 28, 30] and in ten studies participants were under normal daily conditions [21, 27, 29, 31-37]. Among all eighteen identified studies, thirteen administered probiotics to reduce stress symptoms [21-31, 34, 38]. In turn, ten studies assessed the impact of probiotic therapy on reducing the symptoms of depression and/or anxiety [24-26, 32-38]. In five studies the support of cognitive functions/attention through the administration of probiotics was assessed [21, 27, 31, 35, 36].

Table 1. Characteristics of the studies included in the review.
Tabela 1. Charakterystyka badań włączonych do przeglądu.

Study Badanie	Tested parameter Badany parametr	Effect within group Efekt w obrębie grupy	Effect between groups Efekt między grupami	Intervention and dose (CFU) Interwencja i dawka (jtk)	Duration (days) Czas trwania (dni)	Number of participants (active/control) Liczba uczestników (grupa badana/ kontrolna)	Mean age Średnia wieku
Stress studies Badania dotyczące stresu							
Adikari et al. (2020) [21]	Electrodermal responses, heart rate Reakcja skórno-galwaniczna, tętno	–	ns	*Lacticaseibacillus casei Shirota* (3×10^{10})	56	10/9	19.0
Andersson et al. (2016) [22]	Salivary cortisol, salivary immunoglobulin A Kortyzol w ślinie, immunoglobulina A w ślinie	+ +	↓ ns	*Lactiplantibacillus plantarum* 299v (1×10^{10})	14	21/20	18 ÷ 30
Culpepper et al. (2016) [23]	Self-reported stress Samoocena stresu	–	↓ for B. bifidum only, only in sleep-deprived individuals tylko dla B. bifidum w grupie osób z zaburzeniami snu	*Bifidobacterium bifidum* R0071 (3×10^{9})	42	145/147/142/147	19.9
Karbownik et al. (2020) [24]	Salivary cortisol, salivary metanephrine, PSS heart rate Kortyzol w ślinie, metanefryna w ślinie, PSS, tętno,	+ ns +	ns ns ↑	*Saccharomyces boulardii* (5×10^{9})	30	31/29	22.6

Kato-Kataoka et al. (2016a) [25]	Visual analogue stress scale, salivary cortisol, salivary alpha-amylase Wizualna analogowa skala stresu, kortyzol w ślinie, alfa-amylaza w ślinie	– ns	↓ ns	*Lacticaseibacillus casei Shirota* (100×10^9)	56	23/24	22.8
Kato-Kataoka el.al. (2016b) [26]	Salivary cortisol, salivary immunoglobulin A Kortyzol w ślinie, immunoglobulina A w ślinie	–	ns	*Lacticaseibacillus casei Shirota* (100×10^9)	56	24/23	22.9
Kelly et al. (2017) [27]	PSS, self-reported stress SECPT cortisol SECPT PSS, kortyzol SECPT, samoocena stresu SECPT	ns –	ns ns	*Lacticaseibacillus rhamnosus* (1×10^9)	28	15/14	24.6
Marcos et al. (2004) [28]	Serum cortisol Kortyzol w surowicy	–	ns	*Lactobacillus delbrueckii subsp. bulgaricus / Streptococcus salivarius thermophilus Lacticaseibacillus casei* DN114001 (1×10^9)	21	73/63	18-23
Moller et al. (2017) [29]	Blood pressure, PASAT Ciśnienie krwi, PASAT	–	ns	The mix of 8 strains Mieszanka 8 szczepów ($112,5\times10^9$)	14	57/48	20.2
Nishida et al. (2017) [30]	Salivary cortisol Kortyzol w ślinie	–	↓	*Lactobacillus gasseri* CP2305 (1×10^{11}) (paraprobiotic)	84	34/35	25.0

Papalini et al. (2019) [31]	Visual analog scale, salivary cortisol, salivary alpha-amylase, heart rate, blood pressure Wizualna skala analogowa, kortyzol w ślinie, alfa-amylaza w ślinie, tętno, ciśnienie krwi	+	ns	The mix of 9 strains Mieszanka 9 szczepów (2.5×10^9)	28	29/29	21.5
Salleh et al. (2021) [34]	PSS	ns	↓	*Lacticaseibacillus casei Shirota* (3×10^{10})	42	15/15	19.7
Venkata-raman et al. (2021) [38]	Serum cortisol, PSS Kortyzol w surowicy, PSS	<	↓	The mix of 6 strains Mieszanka 6 szczepów (2×10^9, 1×10^9)	28	36/38	21.4
Anxiety / Depression studies Badania dotyczące lęku / depresji							
Karbownik et al. (2020) [24]	DASS, STAI	<	ns	*Saccharomyces boulardii* (5×10^9)	30	31/29	22.6
Kato-Kataokal.t al. (2016a) [25]	STAI	–	ns	*Lacticaseibacillus casei Shirota* (100×10^9)	56	23/24	22.8
Kato-Kataol. et al. (2016b) [26]	STAI	–	ns	*Lacticaseibacillus casei Shirota* (100×10^9)	56	24/23	22.9
Qin et al. (2021) [32]	Hamilton Depression Rating Scale and Hamilton Anxiety Scale Skala Depresji Hamiltona i Skala Lęku Hamiltona	<	↓	Bifidobacterium longum subsp. longum (1.2×10^{10})	15	60/60	18-24

Rianda et al. (2022) [33]	Children's Depression Inventory Inwentarz depresji dziecięcej	–	↓	*Limosilactobacillus reuteri* DSM17938 / *Lacticaseibacillus casei* CRL431 ($5×10^8$)	18	53/70/55/60	11-18
Salleh et al. (2021) [34]	The Brunel mood scale and CSAI-2 Skala nastroju Brunela i CSAI-2	ns	↓	*Lacticaseibacillus casei Shirota* ($3×10^{10}$)	42	15/15	19.7
Slykerman et al. (2018) [35]	CES-DC	–	ns	*Lacticaseibacillus rhamnosus* HN001, *Bifidobacterium animalis subsp. lactis* HN019 ($6×10^9$)	751 *	109/118/115	11
Steenbergen et al. (2015) [36]	BDI-II, BAI	ns	↓	The mix of 9 strains Mieszanka 9 szczepów ($2,5×10^9$)	28	20/20	19.9
Tran et al. (2019) [37]	BAI PSWQ	–	ns (BAI total) ↓$50 × 10^9$ CFU only ns (BAI ogółem) ↓ tylko dla $50 × 10^9$ jtk	The mix of 10-15 ($10-20×10^9$) and 16-20 strains ($40-50-20×10^9$) Mieszanki 10-15 ($10-20×10^9$) i 16-20 szczepów ($40-50-20×10^9$)	28	14/13/11/15/15	20.6

Venkataraman et al. (2021) [38]	DASS, STAI	<	↓	The mix of 6 strains Mieszanka 6 szczepów (2×10^9, 1×10^9)	28	36/38	21.4
Cognition / Attention studies / Badania dotyczące funkcji poznawczych i uwagi							
Adikari et al. (2020) [21]	DVT-RT	+	↓	*Lacticaseibacillus casei Shirota* (3×10^{10})	56	10/9	19.0
Kelly et al. (2017) [27]	CANTAB	+	ns	*Lacticaseibacillus rhamnosus* (1×10^9)	28	15/14	24.6
Papalini et al. (2019) [31]	CBCL-AP, emotional face-matching, emotional face-word Stroop, color-word Stroop, digit span backward test CBCL-AP, emocjonalne dopasowanie twarzy, emocjonalna twarz-słowo efekt stroopa, kolor-słowo efekt stroopa, test wsteczny rozpiętości cyfr	+	ns	The mix of 9 strains Mieszanka 9 szczepów ($2{,}5\times10^9$)	28	29/29	21.5
Slykerman et al. (2018) [35]	CANTAB	–	ns	*Lacticaseibacillus rhamnosus* HN001, *Bifidobacterium animalis subsp. lactis* HN019 (6×10^9)	751*	109/118/115	11
Steenbergen et al. (2015) [36]	LEIDS-r	+	↓	The mix of 9 strains Mieszanka 9 szczepów ($2{,}5\times10^9$)	28	20/20	19.9

Neurodevelopment studies / Badania dotyczące neurorozwoju							
Rianda et al. (2022) [33]	Brain-derived neurotrophic factor Neurotroficzny czynnik pochodzenia mózgowego	–	↓ only for L. reuteri DSM17938 ↓ tylko dla *L. reuteri* DSM17938	*Limosilactobacillus reuteri* DSM17938 *Lacticaseibacillus casei* CRL431 (5×10^8)	18	53/70/55/60	11-18

Explanatory notes / Objaśnienia:
↓: improvement vs. placebo; ↑: diminishment vs. placebo; ns: no significant effect; +: improvement of performance vs. baseline; –: not reported or not applicable;
↓*: poprawa w porównaniu z placebo;* ↑*: zmniejszenie vs. placebo; ns: brak istotnego wpływu; +: poprawa w stosunku do stanu wyjściowego; –: nie zgłoszono lub nie dotyczy;*

*given to mothers from 35 weeks gestation until six months in the case of breastfeeding, given to children from birth until two years
podawany matkom od 35 tygodnia ciąży do sześciu miesięcy w przypadku karmienia piersią, podawany dzieciom od urodzenia do dwóch lat

CFU – colony-forming unit; PSS – Perceived Stress Scale; SECPT – socially evaluated cold pressor test; PASAT – Paced Auditory Serial Addition Test; DASS – Depression Anxiety Stress Scale; STAI – State-Trait Anxiety Inventory; CSAI-2 – The Competitive State Anxiety Inventory-2; CES-DC – The Center for Epidemiologic Studies Depression Scale for Children; BDI II– The Beck Depression Inventory; BAI – The Beck Anxiety Inventory; PSWQ – Penn State Worry Questionnaire; DVT – digit vigilance test; RT – reaction times; CANTAB – Cambridge Neuropsychological Test Automated Battery; CBCL-AP – Child Behavior Checklist – Attentional Problems; LEIDS-r – Leiden Index of Depression Sensitivity-Revised;
jtk – jednostka tworząca kolonię; PSS – skala odczuwanego stresu; SECPT – test zimnopresyjny; PASAT – test seryjnego dodawania bodźców słuchowych; DASS – skala depresji, lęku oraz stresu; STAI – inwentarz stanu i cechy lęku; CSAI-2 – test natężenia niepokoju; CES-DC – skala depresji dziecięcej centrum badań epidemiologicznych; BDI II – skala depresji Becka; BAI – skala lęku Becka; PSWQ – test skali zamartwienia/lęku; DVT – zadanie czujności psychomotorycznej; RT – czas reakcji; CANTAB – zautomatyzowana bateria testów neuropsychologicznych Cambridge; CBCL-AP – lista kontrolna zachowania dziecka – problemy z uwagą; LEIDS-r – Leiden index wrażliwości na depresję – uaktualniony;

In addition, one study examined the effects of a probiotic therapy on neurodevelopment [33]. A variety of stress measures were used, including salivary cortisol, self-reported stress, blood pressure, heart rate, serum cortisol and performance on a behavioral task (Perceived Stress Scale, PSS). Several validated instruments were used to assess anxiety in the studies, such as the Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), and Depression, Anxiety, Stress test (DASS). Finally, a range of assessment tools was used to measure the support of cognition – The Digit Vigilance Test (DVT), The Cambridge Neuropsychological Test Automated Battery (CANTAB), the Leiden Index of Depression Sensitivity-Revised (LEIDS-R), and Emotional Face-Matching, Emotional Face-Word Stroop, Color-Word Stroop and Digit Span Backward Test. The effects of probiotic supplementation on neurodevelopment were studied in two ways, either through The Bayley Scales of Infant and Toddler Development or brain-derived neurotrophic factor (BDNF). The variety of research methods and results obtained from the studies makes it difficult to make direct comparisons between them. Its occurrence is most likely due to the novelty of the field. In future studies, it is important to replicate the findings reported in these studies and to confirm the efficacy and tolerability of the doses, as applicable.

Intervention effects

The review revealed mixed results regarding the effects of probiotics on mental health among young people, possibly due to the reasons which were mentioned above.

Stress outcomes

Six of the thirteen studies that measured stress found no significant effects, which could be due to the lack of statistical power [21, 26-29, 31]. In most studies, the number of participants in each arm oscillated around only twenty individuals, which is rather a small number in this type of research [21, 22, 25-27, 31, 34]. However, in a slightly larger study conducted by Nishida et al. [30] paraprobiotics of *Lactobacillus gasseri* CP2305 improved stress and sleep quality in healthy Japanese medical students. Even so, the bacteria strain had been inactivated before consumption, at which point it no longer constituted a probiotic but a postbiotic (formerly paraprobiotic). Compared with the placebo group, paraprobiotics intake significantly reduced the escalation of cortisol levels [30]. A very careful examination of the results led the authors to conclude that the stress-relief effect was related to anti-inflammatory mechanisms, which was the result of changes in the microbiota composition caused by paraprobiotics supplementation. Similarly, Salleh et al. [34] found that with supplementation of probiotic *Lacticaseibacillus casei* Shirota after six weeks, the stress levels of young badminton players significantly decreased by 20 % ($p < 0.001$), but no significant changes were detected in the placebo group. Notably, the same intervention also decreased anxiety levels by 16 % ($p < 0.001$) [34]. In other study [25], the same strain *L. casei* Shirota posed the intervention, but differences in favor of probiotic therapy were observed only for outcomes including IO salivary cortisol levels ($p < 0.05$) [25]. In the same study, another interesting dependence was demonstrated. Milk fermented with *L. casei* Shirota was found to be effective in preserving gut microbiota diversity, and it also alleviated abdominal dysfunction during a stressful period of academic study in healthy medical students [25]. As another example, in a randomized, double-blind, placebo-controlled study, *Lactiplantibacillus plantarum* 299v administered to 41 students with upcoming exams led to a reduction in corticosterone levels after 10 days [22]. In contrast, Karbownik et al. study [24] obtained quite different results, where probiotics (*Saccharomyces boulardii*) were even linked to an increase in heart rate, which could be interpreted as increased physiological stress [24].

According to the reviewed literature, probiotics were found to have mixed results in reducing stress in a young population. Given the wide variety of strains that were tested (Table 1), the efficacy of the strain or taxonomic group cannot be clearly indicated.

Anxiety/depression outcomes

In the case of assessing the impact of psychobiotics on the symptoms of depression or anxiety, in half of the studies, significant differences were noted in favor of the group supplementing probiotics [32, 33, 34, 36, 38]. Qin et al. [32] conducted a study in which a probiotic supplement containing *Bifidobacterium longum* subsp. *longum* was used for anxious college students. The results showed that anxiety decreased in the experimental group compared to the control group after 15 days of intervention [32]. In another study [33] re-enrolled 238 adolescents, 10 years after supplementation with low-lactose milk with either 5×10^8 *Limosilactobacillus reuteri* DSM17938 (n = 55), or either with 5×10^8 CFU/d *L. casei* CRL431 (n = 60). On the Children's Depression Inventory, the "reuteri" group scored 0.38 SD (0.01 ÷ 0.75) ($p = 0.044$) lower than the control group [33]. Similar results were obtained in the [38] study where a multi-strain probiotic or placebo capsules were administered twice a day for 28 days. As a result, students who consumed probiotics showed a significant reduction in their DASS and STAI scores as compared to a placebo group at the end of the trial [38]. Steenbergen et al. [36] hypothesized that the four-week supplementation of multispecies probiotics may act as an adjuvant strategy to ameliorate or prevent depression. It demonstrated a significantly reduced overall cognitive reactivity to sad mood, which was largely accounted for by reduced rumination and aggressive thoughts [36]. It is important to emphasize that even though satisfactory results were achieved in all the studies using supplements containing multiple strains of probiotics [35, 36, 37, 38], the overall results for single strains could not be accurately assessed. On the other hand, no significant differences between the probiotic and placebo groups were noted in the study of Karbownik et al. [24], Kato-Kataoka et al. [25] and Kato-Kataoka et al. [26] in DASS and STAI scores. Curiously enough, a significant difference between the groups in the opposite direction to the expected was reported. In the probiotic group on the CES-DC scale, scores were higher than in the placebo group [35]. The situation looks similar to the effect reported in Tran et al. study [37], in which adverse effects, such as increased BAI scores were observed [37].

Based on all the available literature, probiotics showed mixed results in treating depression and/or anxiety in adolescents and young adults. Thus, it is stated that the literature currently does not definitely support probiotic use in reducing anxiety/depression.

Cognition/attention outcomes

The effectiveness of probiotics in improving cognition was only established in two out of five interventional studies [21, 36]. A decrease in reaction times in the digit vigilance test was demonstrated following 56 days of *L. casei* Shirota administration in young football players [21]. Steenbergen et al. [36] exhibited that a four-week multispecies probiotic intervention reduced self-reported cognitive reactivity to sad mood, as indexed by the LEIDS-r [36]. Moreover, Papalini et al. [31] observed improvements in working memory in the digit span-backward test after the use of multispecies probiotics for 28 days, but only under conditions of acute psychophysical stress [31]. In contrast, other studies [27, 35] did not reveal significant changes in cognition outcomes after the implementation of oral probiotics. Disparities may be caused either by the heterogeneity of the studies or by different strains of probiotics being used. In the study of Slykerman et al. [35], probiotic strains such as *Lacticaseibacillus rhamnosus* HN001 and *Bifidobacterium animalis* subsp. *lactis* HN019 were unassociated with cognitive improvements in adolescents. This study was as interesting insofar as the assessment was conducted after 11 years of probiotics ingestion. Pregnant women consumed one of two preparations of probiotics from 35 weeks gestation until six months in the case of breastfeeding, and their infants received the same treatment from birth to two years. At the age of eleven, the adolescents were assessed for intelligence, executive function, attention, depression and anxiety to determine whether providing probiotics in early life improved their later neurocognitive development [35]. Nevertheless, no benefit was found in either probiotic over the placebo [35].

To sum up, despite several individual studies reporting significant improvements in specific cognitive domains, cumulative results from all studies found no significant effect of probiotics on young people cognition.

Neurodevelopment outcomes

Finally, in one study an attempt was made to determine whether probiotics may contribute to an adolescents' central nervous system (CNS) development and susceptibility to neurological disorders [33]. Rianda et al. [33] evaluated the effect of probiotics supplementation supported with calcium in childhood on the later serum brain-derived neurotrophic factor (BDNF) in adolescents. In the "reuteri" group results were 0.49 SD (0.02 ÷ 0.95) ($p = 0.04$) lower on the serum brain-derived neurotrophic factor compared to the regular calcium intake group [33]. The serum BDNF was used as a tracer neurotrophin for the gut-brain axis [33].

To summarize the evidence on the modulation of the gut microbiota as a potential strategy for neurological disorders and CNS development, despite the hopeful results of quoted study, still seems largely unexplored.

Discussion

Preliminary research failed to find studies referring to the COVID-19 pandemic, using the established PICO research questions, which means that the topic is very fresh and new and that no research results have been published so far. Hence, this systematic review summarized the current evidence about the effectiveness of probiotic-based interventions in managing stress and depression/anxiety as well as improving cognitive and attention abilities, as well as neurodevelopment in humans, including adolescents and young adults.

Assumptions based on the reference of the analyzed results from the time before the pandemic and unrelated to the pandemic are subject to uncertainty and cannot be referred to in a universal way, however, these are the most adequate data currently available. To the best of our knowledge, no studies have been planned or completed till now to assess the impact of probiotic supplementation on the mental health of adolescents affected by the coronavirus pandemic.

Most of the authors agree that it would be disastrous to ignore the immediate and long-term psychological effects of the COVID-19 pandemic, especially among adolescents and young adults. Young people faced fears, uncertainties, substantial changes to their routines, as well as physical and social isolation, alongside a high level of parental stress [2]. Even though not all mental health issues can be prevented, there are steps to ensure child mental health. One of these steps could be the use of psychotropic medications. However, in view of the immense hazards of psychotropic drugs, there has been an ongoing exploration of the possibilities of treating mental disorders using "green" or "natural" alternatives with an acceptable safety profile [39]. Probiotics, when used as psychobiotics, meet this criterion perfectly.

In light of this review's results, it can be concluded that so far there has been limited evidence for the use of probiotics as psychobiotics to reduce stress and depression/anxiety, improve cognition and attention and neurodevelopment in young people. Several factors contributed to these findings – the heterogeneity of treatment, dosage and duration made direct comparisons of interventions difficult. In addition, the way in which outcome measures were conceptualized varied across studies, complicating the assessment of stress, anxiety/depression, cognition, attention and neurodevelopment indices. It is important to note that the authors of the included studies did not use any systematic methodology to assess whether a strain or formulation of probiotics exhibited a psychobiotic effect and each of them chose the assays that they considered to be the most suitable for their study, which resulted in a very variable, heterogeneous array of experiments. In this sense, it leads to a wide range of results (even for the same strains used), which are difficult to compare or classify according to specific criteria. Nevertheless, all probiotic intervention doses seemed similar across cognition/attention, stress and anxiety/depression studies ($1\times10^9 \div 3\times10^{10}$ CFU). The strain that most often appeared in favor of psychobiotic therapy was *Lacticaseibacillus casei* Shirota [21, 25, 26, 33, 34]. Moreover, even this strain had different effects in different studies. For example, in the study of Salleh et al. [34] *Lacticaseibacillus casei* Shirota (with a dosage of 3×10^{10}) was effective in reducing the PSS score, although results of another study [21] revealed that there is no significant difference between the probiotic (*Lacticaseibacillus casei* Shirota with the same dosage), and placebo groups for heart rate and electrodermal responses. Results of another study showed that *Lacticaseibacillus casei* Shirota (3×10^{10}) decreased anxiety levels significantly [34], although the same results were not delivered by both studies of Kato-Kataoka et al. [25] and [26] (both in doses of 100×10^9). On the other hand, in studies that used supplements containing a mixture of probiotic strains [29, 31, 36-38], it was not possible to accurately assess the overall effects of a specific strain. In this case, it is possible that only one of the probiotic strains in the supplement mixture was providing beneficial outcomes or that the net performance was a result of synergistic interactions between several strains in the probiotic mixture in the supplement [36, 40].

Based on the evidence reviewed, it is impossible to recommend a specific intervention that young people could use to improve their mental health that may be affected by the COVID-19 pandemic, i.e. reduce stress, eliminate the risk of anxiety/depression and/or improve cognitive functions and attention.

Merely in one of the eighteen included studies, secondary outcomes included stool bacterial counts [32]. And in turn, two studies conducted assessments of stool properties and/or frequency and/or faecal form and color in accordance with the Bristol Stool Scale (BSS) [23, 30]. As noted by Basso et al. [41] and Cohen Kadosh et al. [12] in their reviews on related topics: "all future studies should include stool sample collections for gut microbial sequencing to assess direct impacts of the intervention on the gut microbiome". Moreover, it would be also useful to assess metabolome of the faeces, however, this was not done in any of the included studies. It is also noteworthy that studies did not account for dietary measures or the consumption of other probiotic products or fermented foods (such as yogurt or sauerkraut). Consequently, it cannot be excluded that the consumption of probiotics was accompanied by spontaneous dietary changes which indirectly accounted for the effect.

The results of the presented review are in agreement with those found in previous systematic reviews and meta-analyses of probiotics intervention on cognitive/ stress/anxiety outcomes in young people. Basso et al. [41] analyzed the effect on anxiety, stress and cognition via both prebiotic and probiotic intake in adolescents and young adults. They emphasized that more research is required to draw out consistency in the effects. That inconsistency was due to non-homogeneity in the trials conducted. They suggested consideration of three key factors in future psychobiotic trials: the specificity of a population sample, the specificity of intervention and homogeneity in outcomes acquired [41]. Cohen Kadosh et al. [12] provided a meta-analysis concerning psychobiotic interventions (prebiotics and probiotics) for anxiety in young people, where extracted post-intervention outcomes as standard mean differences (SMDs) and pooled them based on a random-effects model. Due to the fact that pooled SMD was -0.03 (95 % CI: -0.21, 0.14), there was no effect of psychobiotics to treat anxiety in young people [12]. In turn, a sensitivities analysis demonstrated an SMD of 0.16 (95 % CI: 0.38, 0.07), suggesting that psychobiotics are insufficient in treating human anxiety [12]. For related literature reviews, but including the adult population, Marx et al. [42] got to prebiotics, probiotics and fermented foods and cognitive outcomes. According to the researchers, more than half of the eligible studies reported improved cognitive outcomes following an active intervention, but this evidence was not captured in the meta-analysis, which showed no evidence of beneficial effects [42]. On the other hand, Eastwood et al. [43] in their systematic review of probiotic effects on cognition in all ages, pointed out concerns regarding the quality of the studies although the majority of studies indicated improvements in cognition induced by probiotics [43].

Undoubtedly, the influence of probiotics can even be extended to the brain, affecting psychological well-being and cognitive function. The key here is the gut-brain axis, the bidirectional communication network that links the enteric and central nervous systems. Animal studies provide a compelling illustration of the power of this communication system. Microbiota-depleted rodents, either as a result of an antibiotic therapy or as a result of being raised in sterile environments, exhibit a variety of behavioral defects [4-6]. Strikingly, it is a reversible process, recolonization allows to counteract these effects [44]. It is well known that certain psychiatric and neurodevelopmental disorders can alter the composition of the microbiome in the human body. This is where psychobiotics can come in handy to reconfigure the microbiome to a more preferential profile, with benefits for the brain. The prospect of psychobiotic treatment is exciting, particularly considering the rising prevalence of disorders such as depression following from the COVID-19 pandemic, and the small number of drug discoveries that have taken place over the past few years for such conditions. For this reason, it is worth asking whether psychobiotic interventions in the form of probiotics may be effective in supporting the already fragile mental health of young people, which has been debilitated by the COVID-19 pandemic. The interpretation of the included psychobiotic research requires the consideration of several factors. To measure psychiatric symptoms, a variety of tools are available, making it difficult to summarize the results. In addition, a myriad of product types and effects shown is currently hindering the ability to draw solid conclusions regarding probiotic interventions. It is important to note, however, that this treatment is safe, affordable and less invasive than some sorts of traditional treatment for mental illness. Young patients who resist or do not respond to the standard treatment of depression/anxiety and/or chronic stress may find the ability to modify the microbiota appealing. In addition, thanks to psychobiotics, it will be possible to increase cognitive functions and support the development of adolescents' brain, which is undergoing amazing transformations. Nevertheless, the evidence cited in this review of the literature tempers enthusiasm, and the future will exhibit whether the excitement of the scientific community was justified.

Conclusions

Currently available evidence presented in this review indicates that probiotic interventions are variously effective for supporting cognitive/attentional function, reducing stress, preventing depression/anxiety and/or altering neurodevelopment in adolescents or young adults. The lack of a consistent treatment effect may be attributed to the limited number of studies. The lack of statistically powered studies due to the small study groups and the significant clinical heterogeneity relating to the population, psychiatrics test design and intervention formulation. The future study should be conducted to solve the issues identified. It should be also emphasized, that no studies on psychobiotic interventions in young populations in the light of the pandemic of COVID-19 disease have been found. Nevertheless, research conducted before the pandemic was indirectly related to the current times. A growing number of diagnosed mental problems in the youngest population groups hopefully will force work on finding an effective remedy for the global mental health crisis.

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WPŁYW SUPLEMENTACJI PROBIOTYKAMI STOSOWANYMI JAKO PSYCHOBIOTYKI NA ZDROWIE PSYCHICZNE I SAMOPOCZUCIE DOTKNIĘTE PANDEMIĄ COVID-19 U MŁODZIEŻY I MŁODYCH DOROSŁYCH – PRZEGLĄD LITERATURY AKTUALNEGO STANU WIEDZY

S t r e s z c z e n i e

Wprowadzenie. W czasie pandemii COVID-19 różne czynniki spowodowały dramatyczne zmiany w środowisku życia młodzieży i młodych dorosłych, które doprowadziły do pogorszenia ich samopoczucia i negatywnie wpłynęły na ich zdrowie psychiczne. Dlatego wspieranie zdrowia psychicznego młodych populacji jest nadrzędnym celem badań prowadzonych w ostatnim czasie. Z tego względu, istnieje duże zainteresowanie stosowaniem probiotyków jako psychobiotyków. Przegląd miał na celu uchwycenie aktualnego stanu literatury dotyczącego wpływu suplementacji probiotykami stosowanymi jako psychobiotyki na zdrowie psychiczne młodzieży i młodych dorosłych w świetle pandemii COVID-19. Zakres pracy obejmował systematyczne przeszukiwanie trzech baz danych: PubMed, Web of Science i Scopus oraz bazy badań klinicznych ClinicalTrials.gov.

Wyniki i wnioski. Wstępne poszukiwania nie pozwoliły na odnalezienie opracowań odnoszących się do pandemii COVID-19. Zawężone kwerendy do badań przeprowadzonych przed pandemią pozwoliły zidentyfikować osiemnaście opracowań, których celem było ustalenie, czy suplementacja probiotykami poprawia zdrowie psychiczne młodzieży i młodych dorosłych. We włączonych badaniach najczęściej oceniano wpływ spożycia probiotyków na poziom stresu, objawy depresyjne, funkcje poznawcze i neurorozwój. Zgromadzone dowody niejednoznacznie wskazują na skuteczność interwencji probiotycznych w zapewnieniu zdrowia psychicznego dzieci i młodzieży. Wynika to prawdopodobnie z ograniczonej liczby małych i krótkoterminowych badań, a także ich heterogeniczności. Wyniki wyłaniające się z istniejącego piśmiennictwa są zachęcające, jednak nie jest możliwe sformułowanie jednoznacznej rekomendacji. Niezbędne jest zaplanowanie i przeprowadzenie badań nad rolą probiotyków w zapewnieniu zdrowia psychicznego oraz weryfikacja ich skuteczności klinicznej w zwalczaniu negatywnych skutków zdrowotnych wywołanych pandemią koronawirusa, w tym wpływających na zdrowie psychiczne młodzieży i młodych dorosłych.

Słowa kluczowe: pandemia COVID-19; zdrowie psychiczne; probiotyki; psychobiotyki; młodzież