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The brain-gut-microbiota interplay in depression: A key to design innovative therapeutic approaches

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ABSTRACT

Depression is the most prevalent mental disorder in the world associated with huge socio-economic consequences. While depressive-related symptoms are well known, the molecular mechanisms underlying disease pathophysiology and progression remain largely unknown. The gut microbiota (GM) is emerging as a key regulator of the central nervous system homeostasis by exerting fundamental immune and metabolic functions. In turn, the brain influences the intestinal microbial composition through neuroendocrine signals, within the so-called gut microbiota-brain axis. The balance of this bidirectional crosstalk is important to ensure neurogenesis, preserve the integrity of the blood-brain barrier and avoid neuroinflammation. Conversely, dysbiosis and gut permeability negatively affect brain development, behavior, and cognition. Furthermore, although not fully defined yet, changes in the GM composition in depressed patients are reported to influence the pharmacokinetics of common antidepressants by affecting their absorption, metabolism, and activity. Similarly, neuropsychiatric drugs may shape in turn the GM with an impact on the efficacy and toxicity of the pharmacological intervention itself. Consequently, strategies aimed at re-establishing the correct homeostatic gut balance (i.e., prebiotics, probiotics, fecal microbiota transplantation, and dietary interventions) represent an innovative approach to improve the pharmacotherapy of depression. Among these, probiotics and the Mediterranean diet, alone or in combination with the standard of care, hold promise for clinical application. Therefore, the disclosure of the intricate network between GM and depression will give precious insights for innovative diagnostic and therapeutic approaches towards depression, with profound implications for drug development and clinical practice.

1. Introduction

Depression is a common cause of psychiatric disability that affects approximately 5% of the global adult population [1]. People suffering from depression often manifest low mood, anhedonia, irritability, anxiety, sleep disorders, hopelessness, and loss of appetite, which if untreated may ultimately lead to suicide. Disease pathophysiology is multifactorial and arises from a complex interplay between genetic and environmental factors throughout life [2–7]. Although a substantial effort has been made to improve the diagnosis and treatment of depression, patient-to-patient variability in terms of response to therapy [8,9] and treatment-related side effects [10–12], together with the delay in antidepressant efficacy [13] remain a concern. Furthermore, the prospect of co-administering traditional psychotherapeutics is hindered by uncertainties about the best combination to choose and safety issues [14,15]. This is mostly due to the absence of effective diagnostic and prognostic markers, which would improve treatment outcomes through patients' stratification and ad hoc therapeutic approaches [16,17].

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Accordingly, the complete understanding of the pathophysiological process behind the onset and progression of depression as well as the identification of novel and effective diagnostic and therapeutic strategies is of utmost importance.

The term gut microbiota (GM) refers to a complex ecosystem composed of bacteria, fungi, protozoa, and viruses that populate our intestines. Under physiological conditions, a balanced intestinal flora ensures the maintenance of homeostasis by strengthening the host immune system, regulating hormonal signaling, and secreting a plethora of metabolites [18,19]. In pathological conditions, however, changes in the relative abundance of the different bacterial species lead to an imbalanced GM community, a condition known as dysbiosis [18]. Several external factors have been linked to intestinal dysbiosis, including dietary habits, drug intake, environmental pollutants, and psychological

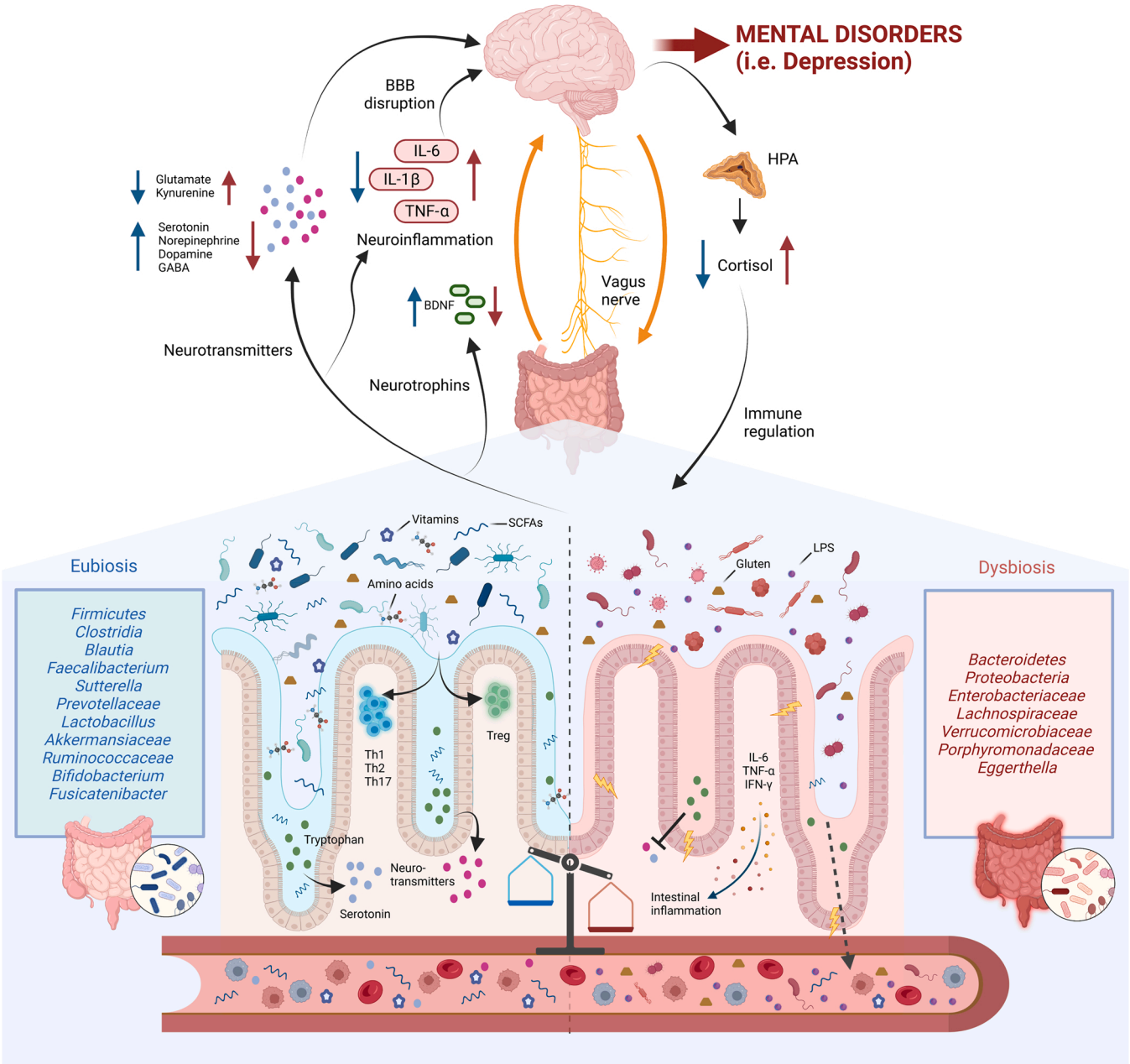

Fig. 1. Gut-microbiota-brain axis in healthy subjects and depressed patients. In healthy conditions (left), a great variety of anti-inflammatory microbes (depicted in light blue and listed in the left box) colonize the gut mucosa and maintain the integrity of the intestinal epithelial barrier by producing several key metabolic products, including SCFAs, vitamins and amino acids. In these conditions, intestinal immunity is reinforced, and adaptive T helper and T regulatory cells are primed for development. SCFAs, vitamins, amino acids, together with serotonin obtained by the conversion of tryptophan at the level of the intestinal epithelium enter the circulation and preserve brain health (blue arrows). In depressed patients, the overgrowth of harmful and pathogenic microbes (depicted in red and listed in the right box), create a dysbiosis condition characterized by gut inflammation and intestinal permeability. Intestinal immunity is not ensured, and the tryptophan metabolic pathway is blocked. Commensal bacteria, their components (i.e., LPS), and other pro-inflammatory molecules (i.e., IL-6, TNF-α, IFN-γ, and gluten) can enter the circulation and disrupt brain homeostasis by reducing the abundance of neurotrophins (such as BDNF), inducing neuroinflammation, and altering the levels of neurotransmitters (red arrows). In turn, altered hormonal signals from the brain modify the cortisol levels and impair the immune system functioning, which is instead reinforced during gut-microbiota-brain axis homeostasis. Abbreviations: BBB: blood brain barrier; BDNF: brain-derived neurotrophic factor; GABA: γ-aminobutyric acid; HPA: hypothalamic-pituitary-adrenal axis; IFN-γ: interferon gamma; IL-6: interleukin-6; SCFAs: short-chain fatty acids; Th: T helper cells; TNF-α: tumor necrosis factor alpha; Treg: T regulatory cells; ↑: increase; ↓: decrease. (Created with BioRender.com).

distress [18,20]. Due to the existence of a complex bidirectional and dynamic crosstalk between the gut and the brain (the so-called gut microbiota-brain axis), an increased understanding of the close relationship has emerged in these last years between GM composition and various neuropsychiatric and mood disorders [21–24]. For example, it has been established that recurrent or early exposure to antibiotics increases the risk of developing psychopathological disorders, including anxiety and depression [25–27]. To date, although some inconsistencies remain, several studies have shown changes in the abundance of various microbial taxa in depressed people compared to healthy controls. Generally, the gut of depressed patients is often characterized by an outgrowth of "pro-inflammatory" bacteria at the expense of the beneficial "anti-inflammatory" species [28,29], similar to what is observed in other diseases [30,31]. Accordingly, an increased relative abundance of *Bacteroidetes* and *Proteobacteria* is reported in major depressive disorder (MDD) patients, with a concurrent reduction in the *Firmicutes* phylum also described [32]. It should be noted that although the *Firmicutes/Bacteroidetes* ratio has been established as a relevant gut health biomarker [33,34], some controversies still exist in using this parameter as a depression-related biomarker [35,36]. These discrepancies may be explained by member-specific changes within these phyla [37], suggesting that a deeper analysis of the differential species may be more indicative in this context.

At the family level, decreased *Ruminococcaceae, Prevotellaceae,* and *Akkermansiaceae* are detected in favor of enhanced *Enterobacteriaceae, Lachnospiraceae, Verrucomicrobiaceae,* and *Porphyromonadaceae* [32, 38–41]. More extensively, different microbial genera, including *Coprococcus, Eggerthella*, *Subdoligranulum, Hungatella, Sellimonas, Sutterella,* and *Eubacterium* have been associated with depression across all the studies [39,41,42]. Among these, *Sutterella* and *Eggerthella* appear to be consistently linked with disease manifestations, with the growth of the first being disfavored over the second in MDD patients [32,39,41,43,44] (Fig. 1).

Often, gut dysbiosis and intestinal inflammation are linked to increased gut permeability (a.k.a. "leaky gut") [45]. Notably, this term refers to a condition in which a loss of the epithelial-barrier integrity allows commensal bacteria and their pro-inflammatory components [i.e., lipopolysaccharide (LPS)] to enter the circulation (metabolic endotoxemia) and trigger systemic inflammation [46,47]. Accordingly, higher serum levels of anti-LPS IgA and IgM deriving from Gram-negative enterobacteria have been reported in MDD patients showing a disrupted intestinal mucosa [48–50]. Other leaky gut biomarkers, such as interleukin (IL)− 6, C reactive protein (CRP), zonulin (a tight-junction modulator), LPS binding protein, and intestinal fatty acid binding protein (which is released upon gut mucosal damage) have also been associated with depression in independent studies [51–53]. These events, together with the notion that an increased enterobacterial translocation triggers the activation of oxidative and nitrosative pathways [50,54], lead to the establishment of an immune-inflammatory status typically found in depression [55,56]. Indeed, it should be kept in mind that the interplay between bacterial species and the gut mucosal immune cells is crucial to maintain the correct balance within the mucosal immune system [57]. For example, T regulatory and T helper (Th1, Th2, and Th17) cells are primed for development in the gut thanks to signals generated by the GM, thus fostering adaptive immunity [58–60].

GM also exerts fundamental metabolic functions. These include the production of short-chain fatty acids (SCFAs, such as propionate, butyrate, and acetate), the synthesis of neurotransmitters [i.e., serotonin, glutamate, γ-aminobutyric acid (GABA)], the transformation of bile acids by bacterial enzymes as well as the production of vitamins, amino acids, and amino acids-related metabolites [42,61–64], which in turn contribute to the healthy activity of many organs, including myocardial function [65], metabolism [66], and brain homeostasis [67]. Interestingly, some of these microbial-derived metabolites [e.g., folate, butyrate, choline, and trimethylamine-N-oxide (TMAO, a product of choline metabolism linked to brain damage and neurodegeneration)] can also act by modulating histone modifications, DNA methylation, and non-coding RNA-associated gene silencing, thus acting as epigenetic factors [68]. It has been reported that SCFAs and secondary bile acids (glycolithocholic acid, taurolithocholic acid, and lithocholic acid 3-sulfate) are decreased in MDD patients, while the serum levels of TMAO correlate with the symptomatology of depression [32,69–71]. Of note, the supplementation with SCFAs in animal models of brain damage and vascular depression improves hippocampal neurogenesis, preserves blood-brain-barrier integrity, and ameliorates depression-like behavior, possibly by favoring the tryptophan conversion into serotonin over kynurenine (whose production is instead favored in the context of depression) [72,73].

While several studies have been conducted to understand the potential therapeutic role of GM in the context of depression, the actual benefit of these approaches (alone or as adjuvant therapies) remains unclear, partly due to conflicting data obtained from independent studies. Furthermore, the search for GM-related biomarkers focused on the early detection of depression remains largely unexplored. Here, we summarize the main microbial markers linked to disease onset and progression and provide evidence for potential clinical implementation of the standard therapy with GM-based approaches, with a particular focus on prebiotics, probiotics, specific dietary habits, and fecal microbiota transplantation (FMT). Potential synergistic and/or antagonistic effects derived from the combination of these strategies are also discussed to foster clinical development.

2. Mutual relationship between gut microbiota and antidepressants

Although GM-based therapeutics represent promising avenues to treat depression, antidepressants remain the standard of care. Currently, the most prescribed antidepressants are selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), serotonin antagonist and reuptake inhibitors (SARIs), and noradrenergic and specific serotonergic antidepressants (NASSA). To date, extensive studies have been made to prove their efficacy and characterize the related side effects [74], but the precise mechanism of action is not entirely defined. Recently, the bidirectional interaction between GM and drug intake has emerged as a key modulator of antidepressants' pharmacokinetics and pharmacodynamics [75,76]. Indeed, while changes in the GM composition influence drug absorption, metabolism, and activity, neuropsychiatric drugs can shape the intestinal flora by altering the abundance of specific taxa [23,75,76] (Fig. 2). One of the first pieces of evidence came in 2000 when Munoz-Bellido et al. reported that SSRIs exert antimicrobial activities (mainly towards Gram-positive species) by blocking the function of efflux pumps [77]. To date, these bacteriostatic and bactericidal properties have been extended to other classes of antidepressants, among which are TCAs [78]. In this respect, in vitro testing of desipramine revealed a potent antimicrobial activity against 12 commensal bacteria including *Bifidobacterium animalis*, *Akkermansia muciniphila*, and *Bacteroides fragilis*, which are normally well-represented in the human intestinal flora [78]. Among SSRIs instead, while fluoxetine significantly inhibits the growth of both *Lactobacillus rhamnosus* and *Escherichia coli*, escitalopram's antimicrobial activity is more potent towards the latter, at least in vitro [79]. Although the antibacterial activity of antidepressants may mediate their clinical benefits, it can also be of concern. For instance, it has been reported that SSRIs and TCAs exert selective pressure for bacterial variants with enhanced efflux pump activity, thus promoting antibiotic resistance [80]. Similarly, antidepressant exposure, even for short periods, has been documented to induce antibiotic resistance and persistence by stimulating the expression of stress-related genes and triggering the production of reactive oxygen species [81]. In line with this evidence, chronic unpredictable mild stress (CUMS) depressed rats treated

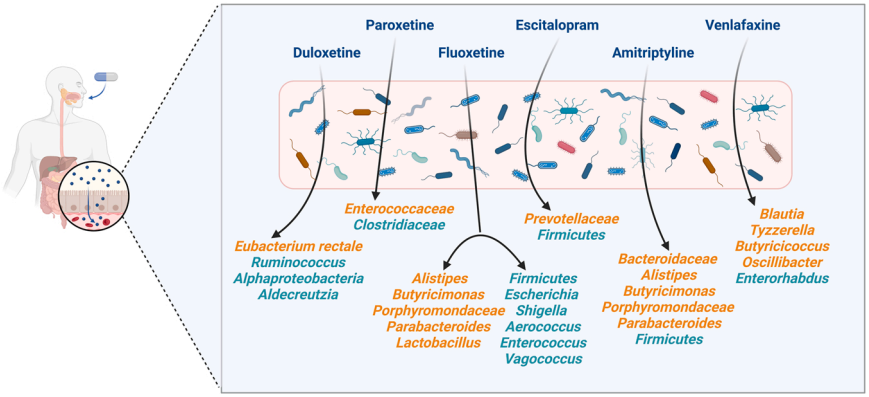

Fig. 2. Mutual interplay between antidepressants and gut microbiota. Antidepressant intake influences the gut microbiota composition by increasing (listed in orange) and decreasing (listed in light blue) certain microbial taxa in a drug-specific manner. (Created with BioRender.com).

with fluoxetine (an SSRI) and amitriptyline (a TCA) showed alterations in the abundance of the antibiotic resistance gene *aph3iiiA*, which mediates aminoglycoside resistance [82]. In light of this evidence, the possible rise of antibiotic resistance among patients treated with antidepressants should not be overlooked. Additionally, antidepressants may shape the GM composition through other mechanisms. Besides exerting a selective depletion of the intestinal flora by antimicrobial effects [83], these drugs can enter bacteria and influence the activity of their metabolic enzymes [84]. This may cause alterations in the microbial secretome, favoring or disfavoring the growth of certain bacterial species whose survival relies on metabolic cross-feeding [84]. Significant changes in the intestinal flora composition were reported in mice and rats treated with different classes of antidepressants, with increased microbial richness and diversity index reported across the studies [85,86]. In particular, while the SSRI paroxetine increases *Enterococcaceae* at the expense of *Clostridiaceae* [87], the SNRI duloxetine increases the abundance of *Eubacterium rectale* and disfavors the growth of *Ruminococcus*, *Alphaproteobacteria*, and *Adlercreutzia* [84,85]. *Bacteroidaceae,* instead, were among the increased microbial families upon amitriptyline intake [82], while fluoxetine, one of the most prescribed SSRIs, was reported to decrease the *Firmicutes/Bacteroidetes* ratio as well as to increase the relative abundance of *Porphyromondaceae* if administered for 6 weeks to a rat model of depression [82]. When considering leaky gut markers, while escitalopram, fluoxetine, and venlafaxine increase ileum permeability [79], sertraline and citalopram improve the intestinal epithelial function by blocking the pro-inflammatory signal mediated by TLR-3 [88]. Taken together, these results indicate that specific antidepressants may perturb differently the gut homeostasis.

There is also evidence that the antidepressant-mediated reshaping of the GM may be important to achieve clinical benefit [89,90]. Accordingly, fluoxetine treatment has been reported to re-establish eubiosis in depressed animals by disfavoring the growth of pathogenic strains such as *Escherichia*, *Shigella, Aerococcus*, and *Enterococcus* while restoring the optimal levels of the anti-inflammatory genus *Lactobacillus* [91,92]. Similarly, venlafaxine-mediated increase in the genera *Blautia*, *Tyzzerella*, *Butyricicoccus,* and *Oscillibacter* as well as a decrease in *Enterorhabdus* improves depressive symptoms by raising the levels of glutamate and serotonin in mice [93]. Mechanistically, the activity of the vagus nerve seems fundamental to achieving a clinical benefit, as blocking this route prevents SSRIs efficacy [94]. In other cases, instead, GM changes following antidepressant treatment appear harmful. Indeed, perturbation of bacterial taxa involved in weight control, such as *Lactobacillus johnsonii* and *Bacteroidales S24–7*, may explain some SSRI-mediated side effects [83]. Other gut-related pathways directly or indirectly altered following antidepressant intake include steroidogenesis, bile acid synthesis, signal transduction, carbohydrate metabolism, and membrane transport [82,87,95]. However, more studies are needed to elucidate the beneficial or harmful impact of these changes within the context of depression.

To date, few studies, mostly on escitalopram, have been conducted to unravel the relationship between antidepressants and GM in humans. Overall, increased α-diversity and reshaping of the GM have been reported in MDD patients following escitalopram treatment, although the limited cohort analyzed may determine some inconsistencies among the studies [96,97]. Specifically, and in line with preclinical evidence, escitalopram modifies the GM of MDD patients towards a decreased *Firmicutes/Bacteroidetes* ratio and an increase in *Prevotellaceae* [96]. Metabolically, data obtained from 290 MDD patients treated with citalopram (the racemate) or its S-enantiomer escitalopram revealed an association between SSRIs and alterations in the metabolic profiles of tryptophan, purine, and tyrosine pathways [98]. In more detail, these include a reduction in xanthine and hypoxanthine production and an increase in the abundance of indoles, 4-hydroxybenzoic acid, and 4-hydroxyphenyl acetic acid. Moreover, higher serotonin levels were reported among responders compared to non-responders, suggesting the feasibility of using metabolites related to the microbiota-gut-brain axis as treatment-response biomarkers for depression [98].

On the other hand, GM composition can, in turn, influence the effectiveness or even the toxicity of specific drugs [84] (Fig. 2) via either chemical and metabolic transformation of the ingested medications (a.k.a. biotransformation) or intracellular storage of drugs without processing (a.k.a. bioaccumulation) [84,99]. In this regard, it has been reported that GM composition determines duloxetine bioavailability by regulating its bioaccumulation [84,99], while the interaction between intestinal microbes and venlafaxine may explain its delayed activity [100]. In the case of duloxetine, the co-administration of *Ruminococcus flavefaciens* abolishes the therapeutic benefits achieved by duloxetine alone in preclinical studies [85]. Similarly, fluoxetine's efficacy greatly decreases in healthy mice transplanted with a "depressed microbiota" because of altered tryptophan metabolism and serotonin biosynthesis [101]. Ketamine, an N-methyl-D-aspartate receptor antagonist, is also affected by GM composition [102]. Accordingly, the relative abundance of *Deltaproteobacteria*, *Mollicutes*, and *Butyricimonas* determine ketamine's activity in depressed mice [103], and higher levels of *Actinobacteria* and *Coriobacteriia* have been proposed as biomarkers for ketamine efficacy in an independent study [104].

As drug resistance following antidepressant intake is of concern [105], the discovery of new predictive and prognostic biomarkers is of major interest. In this context, antidepressant-induced GM alterations may be used to discriminate susceptible from resistant subgroups [106,107]. In this respect, it has been shown that increased levels of *Prevotellaceae_UCG-003* and decreased abundance of *Ruminococcaceae* and *Lactobacillaceae* discriminate escitalopram's responder mice from their non-responder counterpart [86]. Although still limited, human studies have also identified some microbial taxa differentially expressed

between responders and non-responders. Among these, *Tenericutes*, *Proteobacteria*, and *Peptostreptococcaceae* have been positively correlated with MDD-treatment resistance, while higher levels of *Actinobacteria* are common among responders [108]. Moreover, the relative abundance of *Clostridium perfingens* has been proposed as a predictive biomarker of treatment resistance towards antidepressants as well as anxiolytics [107]. In this context, the pro-inflammatory features of *Clostridium perfingens* as well as its toxin-producing capability may offer insights into the mechanisms underlying therapeutic resistance.

Overall, the mutual influence between GM composition and antidepressant intake has been evidenced by numerous studies. However, only a few have been conducted on human cohorts, often in an observational setting. Given the clinical need for more suitable antidepressants, further studies are encouraged to implement innovative predictive and prognostic biomarkers as well as to improve drug efficacy while limiting side effects.

3. Gut microbiota-based interventions: probiotics

3.1. Preclinical studies

The World Health Organization defines probiotics as living microorganisms that when consumed in adequate amounts are beneficial for the host [109]. Although nowadays the use of probiotics is widely prevalent, their actual preventative and therapeutic role against a wide range of diseases remains to be clarified [110]. Concerning psychological disorders, several preclinical studies have shown that probiotics supplementation attenuates depression by reshaping the GM composition and regulating the abundance of SCFAs [111]. In particular, amelioration of depressive behavior, increased social interaction, and reduced anxiety have been reported upon probiotics administration to mice and rats subjected to CUMS or social defeat stress [112–119]. The probiotics administered in these studies include *Lactococcus lactis* [114], *Lactobacillus paracasei (L. paracasei)* and *L. rhamnosus* [115,120,121], *Akkermansia muciniphila (A. muciniphila)* [119], *L. paragasseri* [117], *L. kefiranofaciens* [118], *L. plantarum* [122], *Bifidobacterium breve* [113, 123], and multi-strain probiotic formulations containing different species of *Bacillus, Lactobacillus*, and *Bifidobacterium* [112]. Of note, the behavioral benefits were accompanied by increased hippocampal levels of norepinephrine, serotonin, and brain-derived neurotrophic factor (BDNF), decreased serum corticosterone and adrenocorticotropic hormone, as well as improved neurite outgrowth in the dentate gyrus [112, 114–119,123,124]. At the intestinal level, reduced gut dysbiosis and constipation, increased α-diversity, re-established plasma levels of tryptophan and tryptophan metabolites, and enriched fecal abundance of SCFAs (particularly acetate and butyrate) were reported in depressed animals receiving probiotics compared to their untreated counterparts [112,114,118]. Generally, an increased relative abundance of *A. muciniphila*, *Bifidobacterium,* and *Lactobacillus* to the detriment of the *Bacteroidia* class seems to mediate the benefits linked to probiotics intake [113,117]. Nevertheless, the activity of probiotics towards increased or decreased *Firmicutes/Bacteroidetes* ratio remains unclear, pointing to a possible probiotic strain-specific modulation of the GM [112,114].

The robustness of these data is demonstrated by the fact that very similar results have been reported also in other animal models of depression, including *E. coli*-induced depression [125], alcohol-mediated depression [126], and corticosterone-induced chronic stress [127]. When taken together, all these studies indicate that probiotics mediate intestinal and brain benefits through the modulation of neuroinflammation and oxidative stress [112,113,128]. According to this concept, probiotics-induced reshaping of the GM re-establishes eubiosis and intestinal barrier integrity, thus preventing LPS from entering the bloodstream and triggering systemic inflammation [126]. This results in reduced levels of brain IL-1β and tumor necrosis factor-alpha (TNF-α), an increased hippocampal abundance of BDNF+ /NeuN+ (a marker of postmitotic neurons), less NF-kB+ /Iba1 + (a microglial marker) and IL-1R+ cells, and re-established levels of serotonin, which accounts for anti-depressive effects [125,126]. Despite these promising results, however, some discordant studies indicate that the strain choice is probably fundamental to achieving sufficient therapeutic efficacy, as some probiotic strains may be beneficial or harmful depending on the context [129].

3.2. Clinical studies

Concerning the clinical studies, systematic reviews and meta-analyses report an overall significant amelioration of depressive symptoms upon probiotics intake [130–134]. Particularly, patients with mild to moderate depression show the greatest mental benefits, indicating that patient stratification should be considered when prescribing probiotics [135]. Data obtained from randomized controlled trials point out that probiotics consumption among depressed individuals is associated with decreased Hamilton Depression Rating Scale (HAMD) scores, reduced inflammation, and improved antioxidant capacity (measured as CRP, IL-10, and malondialdehyde levels) [136]. However, study-to-study variability in strain, timing, and dosages may sometimes lead to contrasting evidence and discordant results [135]. Here the most important and used probiotics are reviewed.

3.2.1. Bifidobacterium longum and Lactobacillus helveticus

Bifidobacterium and *Lactobacillus* are well-known probiotics that have been widely considered as preventative and therapeutic approaches across a range of physiological and pathological conditions, regardless of the recipient's age [137–141]. To date, extensive research has been carried out to unravel their possible prescription in patients suffering from psychological disturbances [142–169] (Table 1).

The use of *B. longum* as a possible therapeutic intervention against depressive symptoms emerged in 2017, when Pinto-Sanchez et al. first showed that a 6-week *B. longum* administration to patients suffering from intestinal bowel syndrome (IBS) reduces the depression score and induces changes in brain activity compared to the placebo-control group, with persistence of effect at 10-week follow-up [142,170]. In the context of MDD, promising results have been obtained upon co-administration of *B. longum* together with *L. helveticus* [151]. Indeed, data coming from a randomized controlled trial conducted on 81 MDD patients with low-to-moderate depression showed that an 8-week co-treatment with *B. longum* and *L. helveticus* is sufficient to significantly reduce depression (as measured by the Beck Depression Inventory score) compared to groups treated with prebiotics or placebo [151]. These benefits were accompanied by an increased ratio of circulating tryptophan/isoleucine [151], which is known to inversely correlate with symptom severity [171]. Furthermore, *post-hoc* analysis performed on the same cohort reported that patients treated with probiotics show a significant increase in BDNF and appetite, although no differences in body mass index or weight were noticed compared to controls [152, 153]. These results were then confirmed by an independent open-label pilot study involving 10 treatment-naïve MDD patients with moderate levels of depression [154]. In this study, the combined administration of *B. longum* and *L. helveticus* (3 ×10^9 CFU) daily for 8 weeks significantly improved sleep quality and reduced depression with no adverse events [154]. However, the results obtained from a previous independent double-blind, randomized controlled trial showed no improvements in mood or other disease biomarkers in similar treatment conditions [155]. This discrepancy may be due to differences in symptom severity, disease chronicity, and antidepressant medications between the two studies [155] and may also suggest the need of combining antidepressants and probiotics to achieve more substantial benefits.

3.2.2. Lactobacillus plantarum

L. plantarum is a lactic acid bacterium characterized by adaptability to different ecological environments, genome plasticity, and the

Table 1
Clinical evidence on the use of probiotics in depression.

Probiotic	Strain	Type of study	Cohort	Study design	Results	Ref.
Bifidobacterium longum	NCC3001	RCT, identification n° NCT01276626	IBS/diarrhea patients + depression/anxiety (mild to moderate)	6 weeks: • Probiotic (n = 22) • Placebo (n = 22)	↓ Depression ↑ Quality of life ↓ Limbic reactivity = Anxiety	[142]
	N/A	RCT	Healthy undergraduate students	1 week: • Probiotic (n = 40) • Placebo (n = 39)	= Anxiety = Stress = Depression	[143]
Bifidobacterium breve	CCFM1025	RCT, identification n° ChiCTR2100046321	MDD	4 weeks: • Probiotic + SSRI (n = 40) • Placebo + SSRI (n = 39)	↓ Depression ↓ GI discomfort ↑ Serotonin	[144]
Lactobacillus plantarum	299 v	RCT, identification n° NCT02469545	MDD	8 weeks: • Probiotic (n = 20) • Placebo (n = 25)	↑ Cognitive functions ↓ Kynurenine ↑ 3-hydroxykynurenine/ kynurenine = Inflammation = Cortisol	[145]
	HEAL9	RCT, identification n° NCT03932474	Subthreshold/mild-to-moderate depression	6 weeks: • Probiotic + SAMe (n = 46) • Placebo + SAMe (n = 44)	↓ Depression ↓ Anxiety ↑ Cognitive functions	[146]
	PS128	OLT, identification n° N201804031	MDD	8 weeks: • Probiotic (n = 11)	↓ Depression = Inflammation	[147]
		RCT, identification n° NCT04592276	Healthy adults (insomnia)	30 days: • Probiotic (n = 21) • Placebo (n = 19)	↓ Depression ↓ Fatigue ↓ Cortical excitation ↑ Sleep quality	[148]
Lacticaseibacillus paracasei	Shirota	IS, identification n° UMIN000032825	MDD or BD	12 weeks: • Probiotic (n = 18)	↓ Depression ↑ *Actinobacteria* = Inflammation	[149]
Bacillus coagulans	MTCC5856	RCT, identification n° CTRI/ 2015/05/005754	MDD + IBS	90 days: • Probiotic (n = 20) • Placebo (n = 20)	↓ Depression ↓ GI symptoms ↓ Inflammation ↓ Oxidative stress	[150]
Bifidobacterium longum + *Lactobacillus helveticus*	R0175 (*B. longum*) and R0052 (*L. helveticus*)	RCT, identification n° IRCT2015092924271N1	MDD (mild-to-moderate)	8 weeks: • Probiotic (n = 38) • Placebo (n = 36)	↓ BDI ↓ Kynurenine/ tryptophan ↑ Tryptophan/ Isoleucine ↑ Appetite, ↑ Leptin ↑ Energy intake ↑ BDNF ↓ Depression severity	[151] [152] [153]
		OLP, identification n° NCT02838043	MDD (treatment naïve)	8 weeks: • Probiotic (n = 10)	↑ Affective clinical symptoms ↑ Sleep quality	[154]
		RCT, identification n° ACTRN12613000438752	≥ Moderate low mood	8 weeks: • Probiotic (n = 40) • Placebo (n = 39)	= Psychological assessments = Systemic inflammation = BDNF	[155]
	Rosell®− 175 (*B. longum*) and Rosell®− 52 (*L. helveticus*)	RCT	Subthreshold/mild-to-moderate depression	3 months: • Probiotic + SAMe (n = 33) • Placebo (n = 32)	↓ Depression ↑ Quality of life	[156]
Bifidobacterium longum + *Bifidobacterium bifidum*	BORI (*B. longum*) and BGN4 (*B. bifidum*)	RCT, identification n° KCT0003929	Healthy elders (≥65 years old)	12 weeks: • Probiotic (n = 32) • Placebo (n = 31)	↓ Pro-inflammatory gut microbiota ↓ Stress ↑ Mental flexibility ↑ BDNF	[157]

(*continued on next page*)

Table 1 (*continued*)

Probiotic	Strain	Type of study	Cohort	Study design	Results	Ref.
Lactobacillus reuteri + *Bifidobacterium adolescentis*	NK33 (*L. reuteri*) and NK98 (*B. adolescentis*)	RCT, identification n° KCT0004801	Healthy adults (anxiety, depression, and insomnia subclinical)	8 weeks: • Probiotic (n = 78) • Placebo (n = 78)	↓ Depression ↓ Anxiety ↓ IL-6 (serum) ↑ Sleep quality ↑ *Bifidobacteriaceae, Lactobacillaceae* ↓ *Enterobacteriaceae*	[158]
Lactobacillus acidophilus + *Lactobacillus casei* + *Bifidobacterium bifidum*	N/A	RCT, identification n° IRCT2014060717993 N1	MDD	8 weeks: • Probiotic (n = 20) • Placebo (n = 20)	↓ Depression ↓ Insulin (serum) ↓ hs-CRP (serum) ↑ Total glutathione (plasma)	[159]
Lactobacillus rhamnosus + *Bifidobacterium animalis subsp. Lactis*	LGG® (*L. rhamnosus*) and BB-12® (*B. animalis*)	RCT, identification n° IRCT20191127045525N1	Obesity + depressed mood	9 weeks: • Probiotic + $MgCl_2$ (n = 39) • Placebo (n = 35)	↓ CRP = Mood = Intestinal permeability = Cognition	[160]
Bifidobacterium breve + *Bifidobacterium longum* + *Pediococcus acidilactici*	CCFM1025 (*B. breve*), CCFM687 (*B. longum*) and CCFM6432 (*P. acidilactici*)	RCT, identification n° ChiCTR2100046321	MDD	4 weeks: • Probiotic (n = 15) • Placebo (n = 13)	↓ Depression ↓ GI symptoms	[161]
Multi-strain probiotics	9 bacterial strains (Winclove's Ecologic® Barrier)	RCT, identification n° ACTRN12615001081505	Mild-to-severe depression	8 weeks: • Probiotic (n = 34) • Placebo (n = 37)	↓ Cognitive reactivity = Gut microbiota composition	[162]
	14 bacterial strains (Bio-Kult® Advanced, ADM Protexin Ltd)	RCT, identification n° NCT03801655	Mild-to-moderate depression	4 weeks: • Probiotic (n = 35) • Placebo (n = 36)	↓ Depression ↓ Emotional salience ↓ Reward learning = CRP, cortisol	[163]
	PROVIT study: 9 bacterial strains (OMNi-BiOTiC® STRESS Repair)	RCT, identification n° NCT03300440	MDD	4 weeks: • Probiotic + biotin (n = 28) • Placebo + biotin (n = 33)	↓ IL-6 ↑ Butyrate, valine, isoleucine, alanine, lysine, methylamine, sarcosine (feces) ↓ Gallic acid ↑ β-diversity ↑ *Coprococcus* 3 and *Ruminococcus gauvreauii*	[164] [165] [166]
	8 bacterial strains	UCT	Chronic GI symptoms + anxiety/depression	2 months: • Probiotic (n = 83)	↓ Depression ↓ Anxiety ↑ Quality of life	[167]
	8 bacterial strains	RCT, identification n° NCT02957591	MDD	31 days: • Probiotic + standard treatment (n = 21) • Placebo + standard treatment (n = 26)	↓ Depression ↑ Bacterial abundance ↑ *Lactobacillus* ↓ Putamen activation	[168]
	8 bacterial strains (Ecologic®Barrier)	RCT	Healthy subjects	4 weeks: • Probiotic (n = 20) • Placebo (n = 20)	↓ Cognitive reactivity to sad mood ↓ Rumination ↓ Aggressive thoughts	[169]

Abbreviations: BD: bipolar disorder; BDI: Beck Depression Inventory; CRP: C-reactive protein; GD: gluten-containing diet; GFD: gluten-free diet; GI: gastrointestinal; hs-CRP: high sensitivity C-reactive protein; IS: interventional study; MDD: major depressive disorder; N/A: not applicable; OLT: open label clinical trial; RCT: randomized controlled trial; SAMe: S-adenosylmethionine; SSRI: selective serotonin reuptake inhibitors; UCT: uncontrolled trial; ↑: increase; ↓: decrease.

production of antimicrobial compounds (bacteriocins) [172]. Thanks to its great safety profile, *L. plantarum* emerged as a valuable probiotic for a range of gastrointestinal and extraintestinal diseases, including brain-related disorders [173]. In this last regard, there is evidence that the daily administration of *L. plantarum* improves sleep quality, reduces depression, and decreases anxiety in healthy adults [148,174]. Accordingly, results obtained from a 12-week randomized, double-blind, placebo-controlled trial carried out with 103 moderately stressed adults showed that the administration of *L. plantarum* can efficiently improve stress and anxiety, reduce the levels of the pro-inflammatory cytokines TNF-α and IFN-γ, and ameliorate deficits in memory and cognition compared to placebo recipients [174]. Analysis of fecal metagenomes at baseline and the end of treatment revealed a higher Aitchinson distance (a proper distance for compositional data) and a lower Shannon diversity (an indicator of the number of different bacteria found in a stool sample) in the placebo group, which were not observed in the probiotic group [175]. Furthermore, probiotic-treated individuals showed enrichment in the brain-health-related *Faecalibacterium prausnitzii*, *B. adolescentis,* and *B. longum* at the expense of *Roseburia faecis* and *Fusicatenibacter saccharivorans*, in line with re-established levels of the microbial metabolites SCFAs and GABA [175]. Concerning MDD, preliminary data obtained from a small-cohort

open trial showed that *L. plantarum* intake may correlate with improvements in depressive symptomatology (as assessed by lower HAMD-17 and Depressive and Somatic symptoms Scale), despite no changes in circulating pro-inflammatory markers (TNF-α, IL-6, CRP) and zonulin were observed [147]. When tested in combination with other food supplements, *L. plantarum* showed similar psychological benefits [145,146]. In particular, the combined intake of S-adenosylmethionine (SAMe, a natural compound found in the body with also hormone-modulating ability) and *L. plantarum* in patients with mild-to-moderate depression resulted in a fast and efficient reduction of depressive and anxiety symptoms assessed by the Zung Self-Rating Depression Scale in comparison with controls [146]. Unfortunately, the absence of a probiotic-only treated group makes it impossible to determine the potential benefit of *L. plantarum* consumption alone. Nevertheless, based on these data, dietary supplements such as SAMe and different probiotic formulations have been proposed [156,176].

Assessment of synergy and/or antagonism between probiotics and approved MDD treatments is also of interest. In this respect, a recent clinical trial has been performed on patients under standard treatment with SSRIs [145]. In this study, 79 MDD participants were divided into two groups and treated either with SSRIs + *L. plantarum* or with SSRIs + placebo for 8 weeks. The obtained results indicate a significant negative correlation between probiotic intake and kynurenine (a tryptophan metabolite) concentration, which reflects better psychological functions among *L. plantarum* receivers as assessed by the Attention and Perceptivity Test (APT) and the California Verbal Learning Test (CVLT) [145]. In line with other studies, however, no changes in pro-inflammatory (i.e., IL-6, IL-1β, and TNF-α) and stress markers (i.e., cortisol) suggest a different mechanism of action, possibly dependent upon the regulation of GM composition, monoamine neurotransmitters and microbial neuroactive metabolites [145,177,178].

3.2.3. *Bifidobacterium breve*

B. breve is a human-derived bacterium initially isolated from healthy adults. Of note, its probiotic effects are thought to be strain-dependent, as some anti-depressive benefits observed with the CCFM1025 strain are not reported following FHLJDQ3M5 strain administration [179]. This is probably due to a higher niche adaptability, a stronger carbohydrate-usage ability, and a superior metabolic capacity to produce SCFAs and neuroactive molecules, such as tryptophan and hypoxanthine, related to the CCFM1025 strain [179]. Accordingly, evidence from a recent randomized controlled trial conducted on 45 MDD patients showed that a 4-week *B. breve* treatment improves the depressive symptoms [as measured by the HAMD-24 Items and the Montgomery-Asberg Depression Rating Scale (MADRS)] as well as the associated gastrointestinal discomfort compared to the placebo group [144].

Other probiotic bacteria examined for the treatment of MDD include ***Lacticaseibacillus paracasei*** and ***Bacillus coagulans***. Accordingly, while *Lacticaseibacillus paracasei* strain Shirota alleviates depression by contributing to the enhancement of the relative abundance of *Actinobacteria* [149], the consumption of *Bacillus coagulans* among MDD-inflammatory bowel disease (IBD) patients was shown to improve both depressive symptoms (assessed by HAMD, MADRS, CES-D) and gastrointestinal discomfort (assessed by IBS-QOL) by reducing systemic inflammation and oxidative stress [150].

3.2.4. *Multispecies probiotic cocktails*

Multi-probiotic combinations may prove more effective than single bacterial strains in preventing or treating depression, even as adjunctive treatments. The safety, feasibility, and efficacy of these approaches have been investigated in several trials, with promising although sometimes inconclusive results [159,162,180]. There is evidence that a 2-week administration of an 8-strain probiotic formulation (containing strains from the genera *Bifidobacterium, Lactobacillus,* and *Lactococcus*) is effective in reducing anxiety and depression among patients with chronic gastrointestinal discomfort [167]. Similarly, a significant improvement in depressive symptoms (assessed by the HAMD, MADRS, and Brief Psychiatric Rating Scale) as well as in gastrointestinal functions (assessed by the Gastrointestinal Symptom Rating Scale) have been reported in mild to moderately depressed patients treated for 4 weeks with a multi-species probiotic mix containing *B. breve* CCFM1025, *B. longum* CCFM687 and *Pediococcus acidilatici* CCFM6432 [161]. Unexpectedly, these benefits were not associated with changes in the GM composition, suggesting a different mechanism of action [161]. The results obtained from independent randomized, double-blind placebo--controlled trials confirmed a marked amelioration of phycological symptoms upon 4 or 8-week multi-species probiotic uptake [159,163]. Nevertheless, despite these improvements, the ability of probiotic mixtures to improve inflammatory and oxidative stress parameters (i.e., IL-6, CRP, glutathione) remains debated [159,163,164]. When used together with the traditional antidepressant treatment, an 8 strain probiotics mixture (with strains from the genera *Streptococcus, Bifidobacterium,* and *Lactobacillus*) hastened symptoms recovery, promoted the outgrowth of *Lactobacillus*, and preserved the abundance of the beneficial *Prevotella* enterotype, which is usually progressively lost in patients under standard cure alone [168].

It is reported that MDD patients display alterations in fecal metabolites, which reflect changes in the amino acid metabolism [181]. Given that gut microbes possess remarkable metabolic versatility, studies aimed at uncovering metabolic changes upon probiotic intake are of interest. In this respect, results obtained from the PROVIT study (a randomized controlled trial conducted in Austria) showed that 4 weeks of intake of a multi-strain probiotic (composed of *L. casei W56, L. acidophilus W22, L. paracasei W20, L. salivarius W24, L. plantarum W62, B. lactis W51, B. lactis W52, B. bifidum W23,* and *Lactococcus lactis W19*) correlated with a significant increase in fecal SCFAs (butyrate), essential amino acids and related metabolites (Ala, Val, Ile, Lys, sarcosine), and gut-microbiota synthetized molecules (methylamine) [165]. These changes were associated with a higher β-diversity along with an increased relative abundance of *Ruminococcus gauvreauii* and *Coprococcus* 3, which are well-known producers of butyrate (a SCFA with immunoregulatory and anti-inflammatory properties that preserves the intestinal epithelial barrier integrity and prevents brain disorders) [166].

3.3. *Preventative approach*

Probiotics intake among healthy individuals is gaining wider acceptance. According to a nationwide Korean study conducted on 26,118 individuals aged between 19 and 64 years old, dietary-based probiotics consumption inversely correlates with the prevalence of depression, especially in men, suggesting the possibility of administering probiotics far before the onset of clinical depression [182]. Indeed, improvements in mood and reduced negative thoughts were reported among healthy subjects after 4 weeks of intake of a probiotic mix containing *B. bifidum*, *B. lactis*, *L. brevis*, *L. salivarius, L. acidophilus, L. casei,* and *Lactococcus lactis* compared to the placebo group [169]. Moreover, when a combination of *B. longum* and *B. bifidum* was administered to 63 healthy aged subjects (≥ 65 years old) for 12 weeks, significant improvements in mental flexibility, stress, and serum BDNF levels were reported compared to controls [157]. Nevertheless, *B. longum* alone was not linked to any mood, stress, or anxiety improvements when administered for one week to young undergraduates, possibly due to the treatment shortness [143]. Interestingly, the results obtained from an 8-week, double-blind, randomized controlled trial carried out on 156 healthy adults with sub-diagnostic psychiatric symptoms showed a significant reduction in depressive symptoms at 4 and 8 weeks and in anxiety at 4 weeks (as measured by the Beck Depression Inventory score and Beck Anxiety Inventory, respectively), as well as improved sleep quality (assessed by the Pittsburgh Sleep Quality Index and the Insomnia Severity Index) [158]. This study

involved the administration of a probiotic combination composed of *L. reuteri* and *B. adolescentis*, which reflected a GM reshape in favor of the anti-inflammatory *Bifidobacteriaceae* and *Lactobacillaceae* at the expense of the pro-inflammatory *Enterobacteriaceae* species [158].

Although limited, these studies indicate that preventive administration of probiotics against depression holds promise and deserves further investigation.

Overall, these data point to probiotics as promising candidates for the treatment and prevention of depressive symptoms. However, negative results obtained in independent studies [143,160] should not be overlooked, as they may help in identifying the best probiotic strain/-combination and in defining the optimal therapeutic protocol.

4. Gut microbiota-based interventions: prebiotics and symbiotics

An interesting field of current research is focused on the therapeutic potential of prebiotics against depression [183]. The term "prebiotics" refers to molecules deriving from the diet that can be digested by the gastrointestinal microbiota and mediate beneficial effects on individual health by favoring the growth of anti-inflammatory bacterial species over their harmful counterpart [184]. Although the present scientific data cannot be considered definitive as the number of studies is still limited, evidence from the literature highlights controversial results for the use of prebiotics alone as a treatment for depression [185–192] (Table 2). Several studies show that individual prebiotics do not have either a preventive capacity against the onset of depressive disorders [189] or therapeutic effects in patients affected by MDD [151–153,193]. Accordingly, a recent randomized clinical trial pointed out that the intake of the prebiotic lactosucrose does not alleviate symptoms of depression [185]. Similarly, the sole administration of the prebiotic inulin was not related to significant improvements in depressive disorder [187]. Furthermore, a study on the student population tested before the execution of an academic exam showed that prebiotics deriving from the diet do not modify the occurrence of symptoms of depression [194]. Despite all these negative results regarding the use of a single prebiotic, the co-administration of two different types of prebiotics seems to be a more promising strategy against depressive disorders [195]. In this respect, a combination of fructo-oligosaccharides and galacto-oligosaccharides resulted in reduced depressive-like symptoms, higher levels of hippocampal BDNF, and increased cortical serotonin [195,196]. Mechanistically, there is evidence that fructo-oligosaccharides and galacto-oligosaccharides work together in preventing changes in the proportion of *Actinobacteria* and *Proteobacteria*, typical of MDD patients [195,197]. Furthermore, fish oil was demonstrated to restore gut flora eubiosis and to alleviate depressive symptoms in rats [198].

Besides prebiotics co-administration, promising data are emerging on the combinations of prebiotics with probiotics (a.k.a. symbiotics) [132,199] or postbiotics, which consist of inactivated microorganisms or parts of them leading to health improvements [200,201] (Table 2). To date, symbiotic mixtures have been observed to alleviate depressive symptoms not only in murine models of depression but also in a cohort of patients suffering from coronary artery diseases. Of note, the anti-inflammatory effects exerted by these formulations seem crucial in mediating the beneficial action [200,201]. In line with this evidence, a recent large meta-analysis by Hofmeister et al. highlights the efficacy of prebiotics, probiotics, and their combination in attenuating depression-related symptoms [130]. However, despite these encouraging data, much work remains to be done to identify the most appropriate formulations, the adequate amount, and the optimal treatment duration. In addition, the use of more comparable formulations may help to better elucidate the underlying molecular mechanisms and possibly to limit the contrasting evidence currently reported in the literature [130].

5. Gut microbiota-based interventions: fecal microbiota transplantation

During FMT, stool matter from a healthy donor is transferred into the intestine of a recipient patient through colonoscopy/enema, oral pills, or nasogastric/nasoenteric tube route to quickly reshape the GM [202]. The feasibility of this procedure has already been demonstrated for the treatment of *C. difficile* infection, irritable bowel syndrome, and IBD [203,204], and several studies are emerging in the context of neurodegenerative and neuropsychiatric disorders [30,31,205–220] (Table 3).

Several insights into the causality between GM dysregulation and MDD have been provided by FMT studies. For example, stool transfer from depressed IBD, bipolar disorder, or MDD patients to recipient mice resulted in depression-like symptoms, impaired hippocampal neurogenesis, and triggered intestinal inflammation in the treated animals [221–223]. Similarly, transplant of fecal matter obtained from mice exposed to chronic stress caused anxiety, depression, and anhedonia in recipient antibiotics-treated or germ free-mice, mimicking key disease symptoms in humans [224–226]. Mainly, these effects seem to be mediated by *Rikenellaceae*, *Bacteroides fragilis*, *Bacteroides uniformis,* and *Faecalibacterium rodentium*, which are normally abundant in the feces of MDD patients [222,224,227]. Besides triggering colonic, systemic, and hippocampal inflammation through increased levels of the pro-inflammatory cytokines IL-1β, IL-6, IFN-γ and TNF-α [221,225], the "depressed-like" composition of the GM is associated with low synaptic protein levels and altered carbohydrate and amino acid metabolism [37,228]. Accordingly, decreased levels of hippocampal neurotransmitters and alterations in tryptophan metabolites have been reported in rodents receiving stool matter from depressed patients [229,230]. Neuroendocrine modulation is also a mechanism through which the GM influences the onset of depression. Indeed, rats transplanted with a "depressed microbiota" obtained from depressed patients showed increased serum levels of adrenocorticotropic hormone and corticotropin-releasing hormone [229], as normally reported in MDD individuals [231,232]. On the other hand, reduced levels of circulating corticosterone (which is normally upregulated in severe depression) have been observed in "depressed" mice transplanted with a "healthy microbiota" [207]. These data are in line with literature evidence pointing to dysregulations in the hypothalamic-pituitary-adrenal axis response as a key player in the biogenesis of depression [233].

Conversely, transplantation of fecal matter from healthy donors to recipient animal models showing a depressive-like behavior was sufficient to alleviate disease symptoms [221]. Accordingly, various studies reported significant improvements in depression and anxiety tests, reduced gastrointestinal discomfort and increased colonic motility among rats and mice receiving a "healthy microbiota" versus the mock-treated counterpart [205–209,214,234]. These benefits appear to be mediated by a decreased amount of hippocampal glutamate in favor of increased levels of serotonin, BDNF, and GABA, thus re-establishing the correct serotonergic/glutamatergic balance [205,206,214]. Of note, reduced neuroinflammation (measured as decreased brain levels of NF-kB, NLRP3, caspase-1, and IL-1β as well as an attenuated number of $Iba1^{+}$ microglia and $GFAP^{+}$ astrocytes) and a diminished systemic inflammation (measured by serum levels of LPS and IL-6) have been reported across all preclinical studies involving the transplantation of fecal matter from healthy donors to recipient animal models of depression [205–208,214]. This is reflected at the intestinal level by the growth of anti-inflammatory microbial species at the expense of the pro-inflammatory ones, with a consequent improvement in the gut epithelial barrier functions and a reduction in the main intestinal inflammatory molecules (i.e., GLP-1, IL-1β, TNF-α) [205,207,208,214]. When looking at the GM, depressed animals treated with a "healthy" FMT showed a reduction in *Desulfobacterota*, *γ -Proteobacteria,* and *Dialister* sp. in favor of *Lactobacillaceae, Prevotellaceae,* and *Firmicutes,* closely resembling the flora composition of the healthy donors [205–208].

Table 2
Clinical evidence on the use of prebiotics and symbiotics in depression.

PREBIOTICS					
Prebiotic	**Type of study**	**Cohort**	**Study design**	**Results**	**Ref.**
Lactosucrose	RCT, study n° CRB5180010	Depressed patients	24 weeks: • Prebiotic (n = 9) • Placebo (n = 11)	= Depression (MADRS) ↑ Self-efficacy (GSES)	[185]
Inulin	RCT, study n° IRCT20100209003320N15	Obesity + MDD (women, caloric-restriction diet)	8 weeks: • Prebiotic (n = 22) • Placebo (n = 23)	= Depression = Leaky gut = Inflammation	[186,187]
Food-derived prebiotics	PCS	Healthy students	7 days; n = 372: • Fermented food • Food-derived prebiotics	= Cognitive performance = Depression = Anxiety	[194]
Fructo and galacto-oligosaccharides	RCT, study n° NCT04551937	Healthy adults	4 weeks + ≥ 4 weeks washout: • Prebiotic • Control	= Stress = Inflammation = Sleep quality = Depression ↑ *Bifidobacterium*	[188]

SYMBIOTICS						
Prebiotic	**Probiotic**	**Type of study**	**Cohort**	**Study design**	**Results**	**Ref.**
Fructans and galacto-oligosaccharides	Yogurt	PCS	Healthy adults	9.3 years; n = 14,539: • Prebiotic • High-fat yogurt • Low-fat yogurt	↓ Depression (high-fat yogurt) = Depression (prebiotic)	[189]
High-prebiotic diet	Multi-strains probiotic (8 bacterial species)	RCT, study n° ACTRN12617000795392	Moderate psychological distress	8 weeks: • Probiotic (n = 30) • High-prebiotic diet (n = 28) • Symbiotic (n = 32) • Placebo (n = 28)	↓ Anxiety (high prebiotic diet) ↓ Stress (high prebiotic diet) ↑ Mood (high prebiotic diet) ↑ Sleep quality (high prebiotic diet)	[190]
Inulin	*Lactobacillus rhamnosus* G	RCT, study n° IRCT20180712040438N4	Coronary artery disease	8 weeks: • Prebiotic (n = 22) • Probiotic (n = 22) • Symbiotic (n = 22) • Placebo (n = 22)	↓ Depression (symbiotic) ↓ Anxiety (symbiotic) ↓ Inflammation (symbiotic)	[191]
Inulin, fructo and galacto-oligosaccharides	Multi-strains probiotic (4 bacterial species)	RCT, study n° IRCT201704123339N1	Hemodialysis patients	12 weeks: • Probiotic (n = 25) • Symbiotic (n = 25) • Placebo (n = 25)	↓ Depression (symbiotic) ↑ Serum BDNF (symbiotic)	[192]

Abbreviations: BDNF: brain-derived neurotrophic factor; GSES: global self-efficacy scale; MADRS: Montgomery Asberg Depression Rating Scale; PCS: prospective cohort study; RCT: randomized controlled trial; ↑: increase; ↓: decrease.

Table 3
Preclinical and clinical studies on the use of probiotics in depression.

PRECLINICAL STUDIES

Condition	Study cohort/ sample size	Donor	Recipient	Transplantation technique	Results	Ref.
CUMS	SD Rats (n = 30; 10/group)	Untreated rats	CUMS rats	Fecal bacterial fluid gavage (once a week for 3 weeks)	↓ Depression, hippocampal Glu ↓ Serum GLP-1, LPS, IL-6 and intestinal GLP-1 ↑ Colonic motility ↑ Hippocampal 5-HT, BDNF, GABA - Intestinal microbiota ≈ control group	[205]
Depression	Rats (n = 30 FH and 10 SD)	SD rats	FH rats	Fecal fluid inoculation (0.5 mL, 8 times/ day for one day	↑ Hippocampal neurotransmitters ↓ Hippocampal cytokines ↓ Depression ↓ *Dialister* sp. - Intestinal microbiota ≈ donor group	[206]
RS-induced anxiety and depression	Mice (n = 6 *per* group)	Vehicle-treated or RS/ CSS-treated mice	RS mice	Oral gavage of fecal microbiota suspension (0.2 mL) daily for 5 days	↓ Anxiety and depression ↓ NF-kB (hippocampus and colon) ↓ IL-6 and corticosterone (blood) ↓ *Desulfovibrionaceae, γ -Proteobacteria* ↑ *Lactobacillaceae, Prevotellaceae*	[207]
CUMS	SD rats (n = 6 *per* group)	Control rats	CUMS rats	Gavage of 2×10^9 fecal microbiota daily for 2 weeks	↓ Depression ↓ *Desulfobacterota, Bacteroidetes* ↑ *Firmicutes* ↑ ZO-1, occludin ↓ Inflammatory cells (ileum) ↓ NLRP3, ASC, caspase-1, IL-1β (brain)	[208]
CUMS	SD rats (n = 10 *per* group)	Untreated rats	CUMS rats	Gavage of 2×10^9 fecal microbiota daily for 2 weeks	↓ Depression ↑ 5-HT ↓ IL-1β, TNF-α ↓ $Iba1^+$ microglia and $GFAP^+$ astrocytes ↓ NLRP3, ASC, caspase-1, IL-1β (brain)	[214]
CUMS	NLRP3 KO or WT mice	NLRP3 KO mice	CUMS mice	Gavage of 300 μL fecal matter (2×10^8 viable probiotic bacteria) daily for 3 days	↓ Depression and anxiety ↓ Astrocyte dysfunction	[209]

CLINICAL STUDIES

Condition	Study cohort/ sample size	Donor	Recipient	Transplantation technique	Results	Ref.
MDD	Case study (n = 2)	Healthy donors	Women (50 and 60 years old) under usual anti-depressive therapy	30 frozen capsules (orally) each containing 8.25 g donor stool	↓ Depression 4 weeks after FMT ↓ Constipation - Only transient amelioration	[215]
MDD and anxiety	Phase 1, open-label trial (n = 12)	Healthy donor (25 y.o.)	12 adults with depression, anxiety or both	3 capsules of MET-twice a day *per os* for 8 weeks	↓ Depression and anxiety (75%) over 10 weeks	[216]
IBS, anxiety, depression	Clinical trial (n = 18)	Healthy donor (36 y.o.)	9 IBS patients with anxiety and depression	30 frozen capsules *per os* for 3 times once every other day	↓ Depression, anxiety, and IBS ↓ Fecal isovaleric and valeric acids ↓ *Faecalibacterium, Eubacterium* and *Escherichia* ↑ α-diversity ↑ *Bacteroidetes, Firmicutes*	[217, 218]
Depression	Case report (n = 1)	6-year-old healthy great-grandson	79-year-old woman	200 mL of bacterial solution through gastroscopy	↓ Depression, anhedonia ↑ Weight ↑ *Firmicutes, Lachnospiraceae* ↓ *Bacteroidetes*	[219]
IBS, functional diarrhea, functional constipation, depression, anxiety	Open-label observational study (n = 17)	Healthy donors	Patients with IBS or functional diarrhea or functional constipation and depression/ anxiety	Fecal matter transplantation through colonoscopy	↓ Depression, anxiety ↑ Microbiota diversity	[220]

Abbreviations: ASC: apoptosis-associated speck-like protein containing a CARD (C-terminal caspase-recruitment domain); BDNF: brain-derived neurotrophic factor; CSS: Chaihu-Shugan-San (a Chinese traditional medicine); CUMS: chronic unpredictable mild stress-induced depression; FH rats: Fawn-hooded rats (a depression model); FMT: fecal microbiota transplantation; GABA: gamma aminobutyric acid; GFAP: glial fibrillary acidic protein; GLP-1: glucagon-like peptide-; 5-HT: 5-

hydroxytryptamine (serotonin); Iba1: Ionized calcium-binding adaptor molecule; IBS: irritable bowel syndrome; IL-1β: interleukin 1 beta; IL-6: interleukin 6; KO: knock-out; LPS: lipopolysaccharide; MDD: major depressive disorder; MET-2: bacterial formulation composed of 40 strains; NLRP3: NLR family pyrin domain containing 3; RS: restraint stress; SD rats: Sprague-Dawley rats (healthy controls); TNF-α: tumor necrosis factor alpha; WT: wild type; y.o.: years old; ZO-1: zonula occludens-1; ↑: increase; ↓: decrease.

Although human studies are still limited, promising data are emerging (Table 3). The first evidence of amelioration of psychiatric symptoms upon FMT came from a study involving 17 patients presenting IBS, diarrhea, or constipation. The authors reported a reduction in anxiety and depression following FMT as measured by improved HAMD, HAMA (Hamilton Rating Scale for Anxiety), and QIDS (Quick Inventory for Depressive Symptoms) scores, but the absence of a control group limits the strength of the study [220]. Subsequently, results from a case report conducted on a 79-year-old woman diagnosed with depression and receiving fecal matter from her 6-year-old healthy great-grandson showed the potential of FMT to reduce depression and anhedonia by reshaping the GM [219]. Similar data were also obtained by Doll et al. when using FMT as an additive therapy to the standard of care in two MDD women, although differences in efficacy were observed between

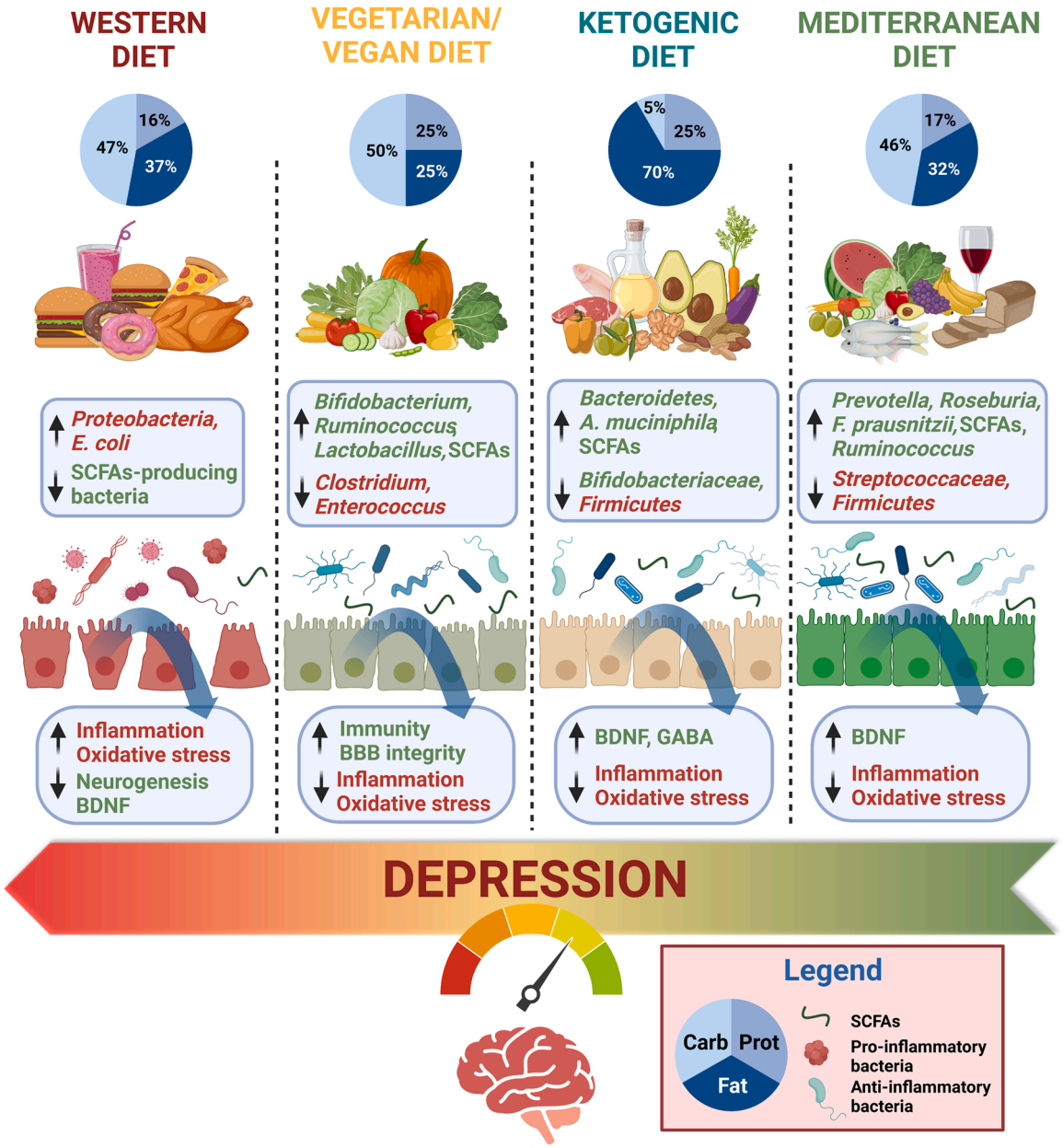

Fig. 3. Dietary habits shape the risk of depression. Diets based on the high intake of calories, saturated fatty acids, and sugars (i.e., Western Diet) are associated with gut dysbiosis by favoring the overgrowth of pro-inflammatory bacteria (listed in red and depicted in red) at the expense of SCFAs-producing species (listed in green and depicted in blue). This triggers a pro-inflammatory state associated with intestinal permeability and sustained systemic oxidative stress (listed in red), with a negative impact on neurogenesis and brain health (listed in green). On the contrary, Vegetarian or Vegan diet, Ketogenic diet, and Mediterranean diet are inversely correlated to the risk of depression by promoting eubiosis, increasing the levels of BDNF and GABA as well as reducing inflammation and oxidative stress. Beneficial microbes and positive effects are listed in green; harmful microbes and negative effects are listed in red. Abbreviations: *A. muciniphila: Akkermansia muciniphila*; BBB: blood brain barrier; BDNF: brain-derived neurotrophic factor; *E. coli: Escherichia coli*; *F. prausnitzii: Faecalibacterium prausnitzii*; GABA: γ-aminobutyric acid; SCFAs: short-chain fatty acids; ↑: increase; ↓: decrease. (Created with BioRender.com).

the two patients [215]. Clinical trial data from 9 depressed IBS patients treated orally with FMT showed marked improvements in both gastrointestinal and psychiatric symptoms, increased microbial diversity, and diminished content of fecal isovaleric and valeric acids, which correlate with FMT efficacy [217,218]. These benefits were paralleled by an increased gut abundance of *Bacteroidetes* and *Firmicutes* at the expense of *Faecalibacterium, Eubacterium,* and *Escherichia* growth, resulting in improved carbohydrate and amino acid metabolism [217,218]. Recently, Meyyappan et al. showed that a bacterial formulation composed of 40 strains obtained from a single healthy donor feces and grown in the lab is safe and tolerable when tested in 12 adults with depression and/or anxiety. Of note, 75% of the participants reported improvements in the MADRS and GAD-7 (7-item Generalized Anxiety Disorder Scale) scores 10 weeks after treatment, with only minor side effects [216]. Given these promising preliminary results, a new phase 2 placebo-controlled trial was announced (identification n°NCT04602715). This study aims at measuring improvements in anxiety, depression, and flora composition as well as at monitoring inflammatory markers in 60 MDD participants aged between 18 and 45 years old receiving the above-mentioned formulation daily for 6 weeks [235]. Similarly, an independent pilot randomized controlled trial has recently been started by Cook et al. to compare allogeneic or autologous FMT via colonoscopy [236]. Although most of the evidence still comes from preclinical studies [213], the results of these trials could prove to be important for better assessing the safety, feasibility, and efficacy of FMT in the context of psychiatric disorders.

6. Gut microbiota-based interventions: diet

The influence of inadequate nutrition on the pathogenesis and progression of several diseases, including neurodegenerative, cardiovascular, and liver disorders, metabolic syndrome, diabetes, as well as mental illness, such as depression, has been well clarified [237–240]. Regarding depression, some cross-sectional and longitudinal studies underscored the association of an unhealthy diet rich in calories, sugars, and saturated fats and poor in fruits, vegetables, fibre, and antioxidants, with an increased risk of disease developing, as well as a rise in symptom severity and chronicity [241–245] (Fig. 3). Furthermore, the relevant role of diet on the gut-microbiota-brain axis, which is shown to be involved in the pathogenesis of psychiatric disorders, including depression, has been well documented [246,247]. Therefore, this evidence, together with other published data reporting the potential role of a healthy diet in reducing depression risk and recurrent depressive symptoms [248–252], suggests that a combination of healthful lifestyle habits [253] and adherence to specific diets, such as the Mediterranean diet (MD) or the ketogenic diet (KD), may protect against the onset of depression.

6.1. Mediterranean diet

The term MD, one of the most worldwide recommended healthy dietary patterns, refers to the dietary habits of the populations surrounding the Mediterranean Sea, which are characterized by a high intake of fruits, vegetables, nuts, cereals, legumes, and olive oil, appropriate consumption of fish, a moderate intake of dairy products, poultry, and eggs, and a low intake of red meat, saturated fat, and wine [254]. Adherence to MD can be effective in the prevention or the co-treatment of numerous pathologies, including cardiovascular [255] and neurodegenerative diseases [256], diabetes [257], metabolic syndrome [258], as well as obesity [259], and psychological disorders, such as depression [260], thanks to its antioxidant and anti-inflammatory nutrients [261,262]. Concerning depression, some MD food components rich in selenium, B, C, and E vitamins, folate, phytoestrogens, magnesium, and omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been shown to have a protective role [263–268]. Although the underlying mechanisms by which MD could prevent depression are not fully determined, recent evidence suggests that the modulation of inflammatory, oxidative stress and gut-microbiota-brain axis pathways could constitute a possible explanation [269], since depressed individuals have been reported to be endowed with an elevated inflammatory state, oxidative stress, and dysbiosis [270,271]. In this respect, evidence highlights a plausible association between the anti-inflammatory and antioxidant potential of MD and depression, as well as the effects of this diet on GM composition and restoration, probably due to a synergistic interaction among dietary nutrients [272–276]. For example, the intake of olive oil, which contains anti-inflammatory bioactive polyphenols and the antioxidant tyrosol, could have neuroprotective effects on mental health by reducing pro-inflammatory cytokines levels (such as IL-1, IL-6, TNF-α, and high-sensitivity CRP), restoring antioxidant defenses, scavenging free radicals, and acting on the metabolism of serotonin and dopamine neurotransmitters by normalizing their levels [277–280]. The consumption of fruits, vegetables, and whole grains, rich in fibres, folate, vitamins B, C, and E, and carotenoids may counteract inflammation and oxidative stress, as well as modulate the intestinal microbiota and the synthesis of neurotransmitters that influence mood, appetite, and cognition [280–282]. The ingestion of eggs, which contain tryptophan, vitamin B-12, folate, and choline, may have a key role in the production of serotonin, dopamine, and norepinephrine [283]. Lastly, the dietary intake of n-3 PUFAs (docosahexaenoic acid, eicosapentaenoic acid, and alpha-linoleic acid), present in fish and vegetable oils, may exert protective effects toward depression risk and depressive mood [284] thanks to their ability to lower the production of pro-inflammatory markers (such as TNF-α, IL-1β, and IL-6), downregulate the hypothalamic-pituitary-adrenal axis, and upregulate neurotrophic factors (such as BDNF), with a crucial role in nervous system development, neuronal differentiation and survival, and cognitive functions modulation [285–287]. Starting from these observations, a considerable number of research groups has conducted cross-sectional and longitudinal studies in young and old individuals with a clinical diagnosis of depression, or with mild to severe depressive symptoms assessed with different methods, to evaluate whether a greater MD adherence is associated with a lower depressive symptomatology and depression incidence [249,250,260,274,280,288–304]. The data obtained from randomized controlled trials are summarized in Table 4 [249,253,260,289,298,304–307]. The findings that emerged from most of these studies showed an inverse correlation between adherence to MD patterns and the risk/symptoms of depression [249,250,260,274,280,288–299]. For instance, Dinu and colleagues reported that individuals with at least one symptom of depression have lower adherence to MD compared to those without this condition, where less than 10% of these subjects consume the ideal amount of fruits and vegetables, while 72% showed an excessive intake of meat and meat products [308]. Furthermore, Oddo and colleagues found a significant association between a greater adherence to MD and a lower probability to manifest moderate to severe depressive symptoms. However, this research group reported a more protective effect of MD on depressed individuals when this diet was associated with healthful lifestyle habits, including decreased smoking rates and alcohol use, and increased physical activity [274]. Similar findings were also described in other studies, yet underscoring the protective influence of the Mediterranean dietary pattern in preventing the development of depressive symptoms [295–297]. For example, Oliván-Blázquez and colleagues observed a higher consumption of an unhealthy diet rich in sweets, red meat, and sugary drinks and lower adherence to MD in patients with subclinical or major depression [295]. Moreover, Sadeghi and co-workers reported a strong association between fruit and vegetable intake and lower odds of depression [297]. Intriguingly, in two PREDIMED (PREvención con DIeta MEDiterránea) randomized trials, it has been documented the beneficial effect of MD supplemented with nuts on the risk of depression in patients with type 2 diabetes, as well as on the content of BDNF [298,305]. In this last regard, patients with depression following MD showed a higher amount of BDNF in the plasma compared with individuals assigned to a control diet

Table 4
Randomized controlled trials on the therapeutic role of Mediterranean diet in depression.

Diet	Type of study	Condition	Study design	Results	Ref.
MD + fish oil	RCT, identification n° ACTRN12614000438651	Self-reported depressed patients	3/6 months: • MD (n = 89) • Control (n = 93)	↓ Depression ↑ Mental health ↑ Omega-3	[260]
ModiMedDiet	RCT, identification n° ACTRN12612000251820.	Moderate-to-severe depression	12 weeks: • ModiMedDiet (n = 33) • Control (n = 34)	↓ Depression (MADRS)	[249, 253]
MD	RCT, identification n° U1111–1242–5215	Moderate-to-devere depression (males)	12 weeks: • MD (n = 36) • Control (n = 36)	↓ Depression (BDI-II) ↑ Quality of life	[289]
MD + VOO/nuts	RCT, identification n° ISRCTN 35739639	High cardiovascular disease risk	3 years: • MD + VOO (n = 1446) • MD + nuts (n = 1293) • Control (n = 1184)	↓ Depression (MD + nuts) ↑ Plasma BDNF (MD + nuts)	[298] [305]
MD + exercise + sleep + sun	RCT, identification n° ISRCTN59506583	Depression	6 months: • Active group (n = 38) • Control group (n = 39)	↓ Depression = Folic acid, vitamin B, magnesium, zinc, selenium, iron	[304]
MD + dairy foods	RCT	Cardiovascular disease risk	24 weeks: • MedDairy (n = 21) • Control (n = 22)	↓ Depression ↑ Cognitive functions = Memory, attention	[306]
MD	RCT, identification n° NCT03081065	Depressed patients in remission	24 weeks: • MD (n = 103) • Control (n = 93)	↑ Mental health ↑ Quality of life	[307]

Abbreviations: BDI-II: Beck Depression Inventory scale-version II; CSS: cross-sectional study; MADRS: Montgomery–Åsberg Depression Rating Scale; MD: Mediterranean Diet; MDD: major depressive disorder; ModiMedDiet: modified Mediterranean diet; VOO: extra virgin olive oil; ↑: increase; ↓: decrease.

[305]. Recent randomized trials also suggest the beneficial role of this diet [249,260,289]. Specifically, in the SMILES (Supporting the Modification of lifestyle In Lowered Emotional States) study patients following MD display a reduction in depressive symptoms [249], while Parletta and colleagues reported a high meat intake and low consumption of MD constituents amongst individuals with depression and found an improvement in mental health in depressed adults assigned to follow MD supplemented with fish oil [260]. Interestingly, medium adherence to the Mediterranean lifestyle (MEDLIFE), which refers to a combination of MD with physical activity, socialization, and adequate rest, is also reported to decrease the risk of depression compared to poor MEDLIFE adherence [309].

However, despite the large encouraging evidence highlighting the positive effect of Mediterranean dietary pattern adherence in preventing the onset of depression or in alleviating the symptoms, a small number of studies report no significant association between the degree of adherence to the MD and the risk of depression [300,302,303]. Possible explanations for these controversial findings could be differences in study design, as well as in methods to assess MD adherence and the degree of depressive symptom severity. In addition, worthy of consideration is the negative study performed by Ibarra and colleagues, which found no significant increase in micronutrient serum levels (such as selenium, magnesium, vitamin B, and folic acid) in depressed patients after six months of MD [304]. Of note, most of these studies focused on the impact of MD on depressive symptoms, especially behavioural ones, whereas to date, no study assessed the effect of this diet on GM in patients with depression. However, in the literature, some studies revealed a promising correlation between adherence to MD and GM modulation [310–315]. Specifically, a study performed on healthy adults showed that individuals with a worse adherence to this diet had a higher *Firmicutes-Bacteroidetes* ratio compared to those with a better adherence [311]. Moreover, De Filippis and colleagues demonstrated the positive impact of MD on increased levels of SCFAs, *Prevotella,* and *Firmicutes*, while Mitsou and collaborators showed adherence to MD is related to a higher *Bifidobacteria-E. coli* ratio, increased prevalence of *Candida albicans*, and acetate [310,315]. Furthermore, another recent study (the NU-AGE project) on 612 non-frail or pre-frail subjects showed that bacterial taxa enriched by a 1-year Mediterranean dietary intervention were negatively associated with the inflammatory markers IL-2, IL-17, and CRP [312]. Lastly, it has also been reported the positive effect of this diet on the GM of obese individuals [313]. Specifically, the authors found that MD administration increases the amount of *Bacteroides*, *Prevotella*, *Faecalibacterium prausnitzii*, *Roseburia,* and *Ruminococcus* [313].

To conclude, although a few studies have not found a clear association between MD adherence and the risk of depression, most of them suggest that adopting a Mediterranean dietary pattern, in association with pharmacological and behavioural therapies, could be a potential supplemental approach to counteract depressive symptoms and even to prevent depression itself. Furthermore, since depression is a multifactorial condition where different subtypes are recognised, it would be important to carry out patient stratification based on particular disease features and design specific treatment programs. Nonetheless, further randomized trials are mandatory to clarify the exact mechanisms behind the beneficial effects of MD adherence in facing depression. Lastly, considering the lack of clinical trials to evaluate the efficacy of MD on the GM composition of depressed individuals, it would be opportune to develop some scientific research to investigate how and whether the Mediterranean dietary intervention could reshape GM constituents and function, and to evaluate whether this approach could be successful in counteracting the development of this psychiatric disability.

6.2. *Ketogenic diet*

The ketogenic diet (KD; a.k.a. keto diet) is a low-carbohydrate, adequate protein, and high-fat dietary regimen that induces a state of ketosis in which ketones, produced from the body's stored fat, are an alternative fuel source to glucose [316]. This diet has a variety of health benefits, primarily including weight loss, improved blood sugar control, and reduced risk of chronic diseases. However, it can also have potential side effects, such as constipation, nutrient deficiencies, digestive issues, changes in blood lipid levels, ketoacidosis, and the "keto flu", a

temporary set of symptoms that can occur when people start KD [317–319].

Although KD was initially developed as a therapy for epilepsy, since it has been shown to reduce seizure frequency by improving seizure control in drug-resistant children and adults [320,321], it has then been explored as a potential therapy for other several conditions, including type 2 diabetes, cancer, obesity, neurodegenerative pathologies, such as Alzheimer's disease and Parkinson's disease [322,323]. Furthermore, recent studies suggest that KD may also have positive effects on psychiatric disorders, particularly on depression [316,317,324]. In this regard, there are a variety of theories about its potential benefits. One of them is related to the fact that the brain of some people suffering from depression is unable to use glucose efficiently as an energy source, leading to a decrease in energy production and mood-regulating neurotransmitters, such as serotonin and dopamine [325]. According to some researchers, reducing carbohydrate intake while increasing fat intake may have beneficial effects on brain function and mood regulation given that the brain adapts to use ketones, which can cross the blood-brain barrier, as an alternative energy source, being this process referred to as ketosis [317].

In addition to the potential benefits of ketones, some animal studies underscored the positive effect of KD on reducing inflammation and oxidative stress [324,326]. For instance, Guan and colleagues, in a mouse model of depression, found that KD has anti-inflammatory and antioxidant effects, and this may contribute to reducing microglial activation in the lateral habenula, a very small brain region involved in mood regulation and reward processing [327]. Another proposed mechanism relies on the modulation of the neurotransmitter systems. Indeed, KD has been shown to increase the levels of the neurotransmitter GABA, which reduces brain neural activity and whose deficiency is often related to anxiety and depression [328]. Besides GABA, KD can also increase the levels of the neurotransmitter glutamate, which is altered in several neuropsychiatric disorders and is involved in key processes such as synaptic plasticity [329]. Lastly, this diet can also increase the production of BDNF, an important protein that promotes synaptic plasticity, neuronal differentiation, and survival, although the mechanism behind this regulation needs to be further elucidated [328,330,331]. Unlike the previously mentioned studies, Huang and collaborators found no significant effects on anxiety and depression in adult naïve mice after 3 months of KD [319].

Some investigations have suggested that KD may alter the composition of the GM, favoring the growth of microbial species able to exploit ketone bodies as a source of energy [325,331–334]. Furthermore, it has been also reported that KD decreases the relative abundance of harmful microbes belonging to the *Firmicutes* phylum (i.e., *Lachnobacterium*) while promoting the proliferation of *A. muciniphila*, a microbial species within the *Verrucomicrobia* phylum [335–337]. Of note, the ability of *A. muciniphila* to degrade mucin and produce SCFAs may account for the benefits associated with KD [338,339]. In another study conducted on children with epilepsy, KD was associated with decreased levels of specific genera such as *Bifidobacterium, Enterococcaceae,* and *Actinomyces* [340]. Although the SCFAs-producer *Bifidobacterium* is a well-known probiotic microbe, its reduction following KD has been reported in several independent studies [341,342]. Since these studies are limited and sometimes discordant, further research is needed for a possible correlation between KD, GM, and depression.

In conclusion, KD may be beneficial for depression through its effects on brain energy metabolism, inflammation, oxidative stress, neurotransmission, and gut microbiota. Despite these promising results, however, further research is needed to better dissect its real benefits.

7. Conclusions

The bidirectional interaction between gut microbiota and depression is emerging as a milestone in defining disease pathophysiology and progression, thus opening the way to innovative clinical applications ranging from diagnosis to treatment. These include the implementation of diagnostic, prognostic, and predictive gut microbiota-based biomarkers as well as new adjunctive therapeutic options aimed at reshaping the gut microbiota composition. Among these, non-invasive and widely acceptable probiotics and dietary interventions (particularly MD) may greatly improve the effectiveness of standard antidepressants while reducing their side effects. It is worth mentioning that neuropsychiatric drugs have long been used, but not without limitations. Indeed, although thousands of patients receive these medications, a considerable portion does not exhibit any clinical benefit, making treatment resistance one of the major concerns about the widespread use of antidepressants. Hence, increasing understanding of the mutual influence between drug intake and gut health will be essential to figure out patient-to-patient variability and even proposing personalized approaches.

When considering gut microbiota-based therapeutics, probiotics, and dietary interventions seem the most clinically advanced strategies. Limitations, however, do exist. Preclinical data can be difficult to interpret because of the great variability in study design, type of animal model, therapeutic intervention, and statistical analysis. Even worse, inter-patient variabilities often pose a bias on clinical trial results, potentially explaining some discordant results. It is well known that age, sex, genetics, lifestyle, dietary habits, comorbidities, social interactions, and emotions greatly affect gut microbiota composition [343–347]. Finally, it should be also considered that MDD patients take multiple medications, which may in turn shape the intestinal flora and impact drug efficacy in a personalized manner. To overcome these limitations, future studies should focus on:

a) Unravel the complex interplay between gut microbiota and antidepressants in patients under polypharmacy, as current studies mostly assessed the intestinal consequences of single antidepressants.
b) Implement innovative and strong predictive and prognostic biomarkers based on the gut microbiota. These may include both the diagnosis of naïve MDD patients as well as monitoring the course and predicting the outcome of therapeutic interventions. Ideal non-invasive specimens to be preferred in this context are blood, feces, and urine.
c) Identify the optimal probiotic formulation for clinical testing. The best dosage and timing should be also defined, and the possible combination with current antidepressants should be considered as well.
d) Assess the clinical benefit of gut-based interventions within different MDD subgroups and relate these data to the severity of the disease.
e) Establish a harmonized FMT clinical protocol employing the optimal delivery method and the best treatment length/periodicity to maximize the benefits while limiting possible side effects.

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