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EXPLORANDO A CONEXÃO MICROBIOTA-CÉREBRO NO TRANSTORNO DEPRESSIVO MAIOR: ALTERAÇÕES NA COMPOSIÇÃO MICROBIANA – MECANISMOS E IMPLICAÇÕES

Vitor Silveira Frank

CAXIAS DO SUL

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Dissertação apresentada ao Programa de Pós-graduação em Biotecnologia da Universidade de Caxias do Sul, como parte dos requisitos para a obtenção de grau de Mestre em Biotecnologia.

Orientador: Prof. Dr. Rafael Colombo
Co-Orientadora: Profa. Dra. Scheila de Avila e Silva

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Explorando a Conexão Microbiota-Cérebro no Transtorno Depressivo Maior: Alterações na Composição Microbiana – Mecanismos e Implicações

Vitor Silveira Frank

Dissertação submetida a banca examinadora designada pela coordenação do Programa de Pós-graduação em Biotecnologia da Universidade de Caxias do Sul, como parte dos requisitos para a obtenção de grau de Mestre em Biotecnologia.

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LISTA DE ABREVIATURAS

OMS	Organização mundial de saúde
AVAIs	Anos de vida ajustados por incapacidade
TDM	Transtorno depressivo maior
HPA	Hipotálamo-pituitária-adrenal
ECL	Células tipo-enterocromafim
GABA	Ácido gama-aminobutírico
IL	Interleucina
TNF	Fator de necrose tumoral
BDNF	Fator neurotrófico derivado do cérebro
CID	Classificação internacional de doenças
CRH	Hormônio liberador de corticotrofina
AVP	Arginina vasopressina
ACTH	Hormônio adrenocorticotrófico
5-HT	Serotonina
DA	Dopamina
NE	Norepinefrina
IMAO	Inibidores da monoamina oxidase
IDO	Indoleamina 2,3-dioxigenase
PCR	Proteína C reativa
ln-hsPCR	Proteína C reativa de alta sensibilidade
IFN	Interferon
iNOS	Óxido Nítrico Sintase Induzível
LPS	Lipopolissacarídeos
TLR	Receptor toll like
NF-kB	Fator nuclear Kappa B
AP-1	Proteína ativadora-1
5HTT	Transportador de serotonina
HTR2A	Receptor de serotonina 2A
TPH2	Triptofano hidroxilase 2
GWAS	Estudos de associação do genoma completo
ADTs	Antidepressivos tricíclicos

ISRS	Inibidores seletivos de recaptação da serotonina
ISRSN	Inibidores seletivos de recaptação da serotonina e noradrenalina
HDRS	Hamilton depression rating scale
STAR*D	Alternativas de Tratamento Sequenciado para Aliviar a Depressão
SNA	Sistema nervoso autônomo
SNE	Sistema nervoso entérico
SNC	Sistema nervoso central
CNS	Central nervous system
CCK	Colecistocinina
QUIN	Ácido quinolínico
SOD1	Superóxido dismutase
MDA	Malondialdeído
NOx	Metabólitos do óxido nítrico
LOOH	Hidroperóxidos de lipídios
AOPP	Produtos proteicos de oxidação avançada
ERO	Espécies reativas de oxigênio
TRP	Triptofano
KYN	Quinurenina
KYNA	Ácido quinurênico
PIC	Ácido picolínico
NAM	Nicotinamida
TDO2	Triptofano-2,3-dioxigenase
KAT	Quinurenina aminotransferase
KMO	Quinurenina 3-monooxigenase
KYNU	Quinureninase
3HAO	Ácido 3-hidroxi-antranílico
NMDA	N-metil D-Aspartato
GLU	Glutamato
ERN	Espécies reativas de nitrogênio
ERO	Espécies reativas de Oxigênio
AGCC	Ácidos graxos de cadeia curta
RN	Recém-nascido
DNA	Ácido desoxirribonucleico

MDD	Major depressive disorder
DALY	Disability-adjusted life years
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
NIH	National Institutes of Health
BMI	Body mass index
HC	Healthy controls
CS	Controles saudáveis
EQ-Vas	EuroQol Visual Analog Scale
PSS	Perceived Stress Scale
LTE-Q	List of Threatening Experiences Questionnaire
CTQ-SF	Childhood Trauma Questionnaire Short Form
BDI	Beck's Depression Inventory
BAI	Beck's Anxiety Inventory
GAD	General Anxiety Disorder scale
HAMA	Hamiton Anxiety Rating Scale
PANSS	Positive And Negative Syndrome Scale
GAF	Global Assessment of Functioning
PHQ	Patient Health Questionnaire
CES-D	Center for Epidemiologic Studies Depression Scale
HCL	Hypomania Checklist
MINI	Mini-International Neuropsychiatric Interview
PROMIS	Patient-Reported Outcomes Measurement Information System
C-SSRS	Columbia Suicide Severity Rating Scale
SITBI	Self-Injurious Thoughts and Behaviors Interview
QIDS	Quick Inventory of Depressive Symptomatology
QIDS-SR	Quick Inventory of Depressive Symptomatology Self-Reported
IDS	Inventory of Depressive Symptomatology
IDS-SR	Inventory of Depressive Symptomatology Self-Reported
MADRS	Montgomery Åsberg Depression Rating Scale
MDQ	Mood Disorder Questionnaire
RDP	Ribosomal Database Project
KEGG	Kyoto Encyclopedia of Genes and Genomes
NCBI	National Center for Biotechnology Information

HOMD	Human Oral Microbiome Database
rRNA	Ácido ribonucleico ribossomal
RefSeq	Reference Sequence Database
ACE	Abundance-based Coverage Estimator
PCoA	Principal Coordinates Analysis
CRP	C reactive protein
HR	Hazard ratio
3-HK	3-Hidroxiquinurenina
SCFA	Short chain fatty acids

SUMÁRIO

RESUMO

Existe uma quantidade de dados cada vez maior estabelecendo uma conexão entre a microbiota intestinal e o desenvolvimento e funcionamento do sistema nervoso central, apontando para um sistema de comunicação bidirecional associado à homeostase intestinal, mas também à certos transtornos mentais, como o transtorno depressivo maior (TDM). O objetivo do estudo foi condensar informações da literatura atual acerca da composição da microbiota intestinal de indivíduos com transtorno depressivo maior comparados à controles saudáveis, com foco na identificação dos filos, ordens, famílias e gêneros diferencialmente abundantes entre esses grupos. Adicionalmente, esses grupos também foram comparados com relação às suas medidas de alfa e beta diversidade. Para a seleção dos estudos, foi realizada uma busca sistemática nas bases de dados PubMed, EMBASE, Web of Science, e PsycINFO de acordo com as diretrizes PRISMA, que resultou na inclusão de 29 estudos, englobando 1352 pacientes com TDM e 1284 indivíduos controle. Essa investigação sugere que não existem diferenças consistentes de alfa diversidade (tanto de riqueza como de uniformidade), entre a população com TDM e a população saudável, enquanto os resultados de beta diversidade se mostraram promissores, porém ainda inconclusivos. Na literatura inclusa, foram destacados como diferencialmente abudantes 80 gêneros, 56 famílias, 14 ordens e 12 filos, variando entre mais ou menos abundante em indivíduos com TDM. Dentre estes, os gêneros *Faecalibacterium, Clostridium*, *Ruminococcus, Dialister, Anaerostipes* e *Roseburia,* as famílias *Oscillospiraceae, Prevotellaceae* e *Bacteroidaceae,* e o filo *Bacillota* se mostraram menos abundantes no TDM. Em contrapartida, os gêneros *Bifidobacterium*, *Oscillibacter* e *Eggerthella*, as famílias *Bifidobacteriaceae* e *Enterobacteriaceae* e o Filo *Actinomycetota* apresentaram maior abundância nesta mesma população de indivíduos com TDM em comparação com o grupo controle. Identificamos ainda que, certos táxons microbianos com capacidade de síntese de ácidos graxos de cadeia curta (AGCC), potencial anti-inflamatório e associados à redução de metabólitos tóxicos da quinurenina estavam consistentemente menos abundantes na população com TDM. De maneira oposta, táxons associados com características pró-inflamatórias, ativação da enzima IDO, e com o direcionamento do metabolismo do triptofano para a síntese de metabólitos tóxicos da quinurenina estavam mais abundantes no grupo TDM em relação aos controles saudáveis. Assim destaca-se os AGCC como moléculas a serem avaliadas com relação ao seu potencial terapêutico, e as vias inflamatória e da quinurenina como possíveis alvos.

ABSTRACT

A growing body of data establishes a connection between the gut microbiota and the development and functioning of the central nervous system, pointing to a bidirectional communication system associated not only with intestinal homeostasis but also with certain mental disorders, such as major depressive disorder (MDD). The objective of this study was to consolidate current literature on the composition of the gut microbiota in individuals with major depressive disorder compared to healthy controls, with a focus on identifying phyla, orders, families, and genera that are differentially abundant between these groups. Additionally, these groups were also compared in terms of their alpha and beta diversity measures. A systematic search of the PubMed, EMBASE, Web of Science, and PsycINFO databases was conducted following PRISMA guidelines, resulting in the inclusion of 29 studies, comprising 1352 MDD patients and 1284 control individuals. This investigation suggests that there are no consistent differences in alpha diversity (both in terms of richness and evenness) between the MDD and healthy populations. In contrast, beta diversity results appear to distinguish between these groups more reliably. Across the included literature, 80 genera, 56 families, 14 orders, and 12 phyla were identified as differentially abundant, varying between being more or less abundant in individuals with MDD. Among these, the genera *Faecalibacterium*, *Clostridium*, *Ruminococcus*, *Dialister*, *Anaerostipes*, and *Roseburia*; the families *Oscillospiraceae*, *Prevotellaceae*, and *Bacteroidaceae*; and the phylum *Bacillota* were found to be less abundant in MDD. Conversely, the genera *Bifidobacterium*, *Oscillibacter*, and *Eggerthella*; the families *Bifidobacteriaceae* and *Enterobacteriaceae*; and the phylum *Actinomycetota* were more abundant in the MDD group compared to the control group. Additionally, we found that certain microbial taxa were consistently less abundant in the MDD population. These taxa included groups that could synthesize short-chain fatty acids (SCFAs), taxa with anti-inflammatory potential, and taxa associated with reducing toxic kynurenine metabolites. Conversely, taxa associated with pro-inflammatory characteristics, IDO enzyme activation, and directing tryptophan metabolism towards the synthesis of neurotoxic kynurenine metabolites, were more abundant in the MDD group than in healthy controls. Thus, SCFAs are highlighted as molecules to be evaluated for their therapeutic potential, and the inflammatory and kynurenine pathways as possible targets.

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1 INTRODUÇÃO

A Organização Mundial de Saúde (OMS) destaca que 3,8% da população mundial sofre de transtorno depressivo, em adultos, este número corresponde a 5% (4% dos homens e 6% das mulheres). Ao todo, 280 milhões de pessoas são afetadas, sendo que anualmente mais de 700.000 mortes são registradas em decorrência de suicídio, causa de morte que ocupa o quarto lugar entre as mais frequentes na faixa etária de 15 a 29 anos de idade (World Health Organization, 2023).

Ao se avaliar os anos de vida ajustados por incapacidade (AVAIs), o transtorno depressivo maior (TDM) se manifesta como a doença mais incapacitante das Américas (Swainson et al., 2019). No Brasil, a esquizofrenia e os transtornos psiquiátricos comuns são responsáveis por mais de 150.000 internações por ano, o que corresponde a um gasto anual médio de R$ 387.634.995 com despesas hospitalares (Carteri et al., 2020). A patologia do TDM ainda não foi completamente elucidada, porém sabe-se que está associada a múltiplos fatores, descritos em diferentes hipóteses. Frequentemente, estas hipóteses apresentam interações entre si. Agrupando a maior parte desses fatores destaca-se: a hipótese monoaminérgica, inflamatória, genética e epigenética, de remodelamento estrutural e funcional do encéfalo, social psicológica e do eixo hipotálamo-pituitária-adrenal (HPA) disfuncional (Cui et al., 2024). Entretanto, existe uma quantidade de dados cada vez maior estabelecendo uma conexão entre a microbiota intestinal e o desenvolvimento e funcionamento do sistema nervoso central, caracterizando um sistema de comunicação bidirecional associado à homeostase intestinal, mas também à motivação e às funções cognitivas superiores. Este sistema é denominado de eixo microbiota-intestino-cérebro, ou simplesmente intestino-cérebro. Nos últimos anos, principalmente a partir de estudos em modelos animais, se observou uma ligação entre a composição da microbiota intestinal e transtornos mentais (Gulas et al., 2018).

Diversos autores têm tentado associar alteração de táxons presentes na microbiota intestinal com a fisiopatologia do TDM. Ferramentas de avaliação na diversidade global de microrganismos como a alfa diversidade, isoladamente, têm apresentado resultados pouco satisfatórios com relação à sua capacidade de distinguir entre indivíduos com TDM e controles saudáveis (Sanada et al., 2020). A beta diversidade, por outro lado, aparenta ser mais promissora em diferenciar entre indivíduos com e sem TDM. Dessa forma, a associação entre essas ferramentas e avaliações de abundância relativa são cada vez mais frequentes (Gao et al., 2023b) (McGuinness et al., 2022).

A interação bidirecional entre o ecossistema presente no intestino e o sistema nervoso, responsável pelo eixo microbiota-intestino-cérebro, é baseada em vias metabólicas, endócrinas, neurais e imunológicas, incluindo o nervo vago, o eixo HPA, mediadores imunológicos, a produção de metabólitos bacterianos e a sinalização enteroendócrina (Góralczyk-Bińkowska et al., 2022). Como exemplo, alguns metabólitos produzidos por certos táxons de bactérias esporulantes atuam como moléculas sinalizadoras na promoção da síntese e liberação de serotonina nas células tipo-enterocromafim (ECL) (Yijing Chen et al., 2021).

Mais especificamente, substâncias envolvidas na comunicação da própria comunidade microbiana intestinal também apresentam efeitos sistêmicos e periféricos no organismo. Estas substâncias também afetam o funcionamento cerebral, como o ácido gama-aminobutírico (GABA) produzido por *Lactobacillus* spp. e *Bifidobacterium* spp., acetilcolina por *Lactobacillus* spp. serotonina por *Escherichia* spp., *Candida* spp. e *Enterococcus* spp., dopamina por *Bacillus* spp. e noradrenalina por *Bacillus* spp. e *Saccharomyces* spp. (Dinan et al., 2014).

Alterações na composição da microbiota intestinal, como o aumento de *Enterobacteriaceae* e *Eggerthela* e a diminuição de *Faecalibacterium* podem se relacionar com o aumento do perfil sistêmico de inflamação, com o aumento de interleucina-6 (IL-6), fator de necrose tumoral-alfa (TNF-alfa) e outros marcadores inflamatórios importantes na fisiopatologia do TDM (Zeng et al., 2016; Forbes et al., 2018; Sokol et al., 2008). Um quadro de inflamação sistêmica em conjunto com o aumento de metabólicos neurotóxicos da quinurenina, estão associados à diminuição de fator neurotrófico derivado do cérebro (BDNF), da neurogênese e com a ativação de vias de sinalização envolvidas com a apoptose no TDM (Stetler and Miller, 2011). Em contrapartida, o aumento de *Roseburia* se relaciona com uma redução da inflamação sistêmica e central (Nie et al., 2021) e redução de agentes tóxicos da via das quinureninas, como o ácido quinolínico (Zhou et al., 2023). Esses resultados, em conjunto, podem indicar um caminho a ser percorrido na investigação das alterações da microbiota intestinal e os seus possíveis efeitos benéficos sobre a função do sistema nervoso central no TDM.

Assim, nesta dissertação, são condensadas informações da literatura atual acerca da composição da microbiota intestinal de indivíduos com TDM comparados à controles saudáveis, com foco nos filos, ordens, famílias e gêneros diferencialmente abundantes entre esses grupos, bem como nas medidas de alfa e beta diversidade.

2 REFERENCIAL TEÓRICO

2.1 TRANSTORNO DEPRESSIVO MAIOR: ASPECTOS GERAIS E DIAGNÓSTICO

O diagnóstico de TDM é baseado em múltiplos critérios, como: a presença de pelo menos 5 sintomas concomitantes que se manifestam consistentemente durante um período de duas semanas e que estabelecem uma mudança em relação ao funcionamento anterior do indivíduo. Tais sintomas podem incluir perda ou ganho significativo de peso (superior a 5% do peso corporal ao mês), insônia ou hipersonia, agitação ou retardo psicomotor, fadiga ou perda de energia, sentimentos de inutilidade ou culpa excessiva ou inapropriada, capacidade reduzida de pensar ou se concentrar, pensamentos recorrentes de morte, ideação suicida recorrente com ou sem plano específico ou tentativa de suicídio. Além desses, necessariamente, um dos dois sintomas a seguir precisa estar presente: humor deprimido na maior parte do dia ou diminuição acentuada de interesse/prazer em quase todas as atividades. Estes critérios buscam enfatizar que os sintomas presentes causam sofrimento clinicamente significativo e garantir que eles não são provenientes de efeitos fisiológicos de substâncias, outros transtornos ou condições médicas (American Psychiatric Association, 2014).

A 11ª edição da classificação internacional de doenças (CID-11) utiliza critérios similares, apresentando pequenas diferenças. Mantém, por exemplo, a exigência de humor deprimido ou interesse diminuído nas atividades diárias, porém, descreve que os sintomas adicionais aparecem em número e intensidade variável. Esclarece que quando muitos, ou quase todos os sintomas estão presentes, sua intensidade pode ser acentuada, enquanto que na manifestação de poucos sintomas, estes se apresentam de maneira intensa. Por fim, destaca também que o indivíduo apresenta sérias dificuldades em seguir com suas atividades na maior parte dos domínios, incluindo o pessoal, familiar, social, educacional, profissional, entre outros (World Health Organization, 2019).

2.2 HIPÓTESES DA PATOGÊNESE DO TDM

Sabe-se que a patologia do TDM está associada a múltiplos fatores comumente agrupados em hipóteses que seguem uma determinada linha de raciocínio, apesar de frequentemente apresentarem interações entre si. As hipóteses monoaminérgica, inflamatória, genética e epigenética, de remodelamento estrutural e funcional do encéfalo, social psicológica

e do eixo HPA disfuncional que agrupam a maior parte desses fatores, estão ilustradas na Figura 1 (Cui et al., 2024).

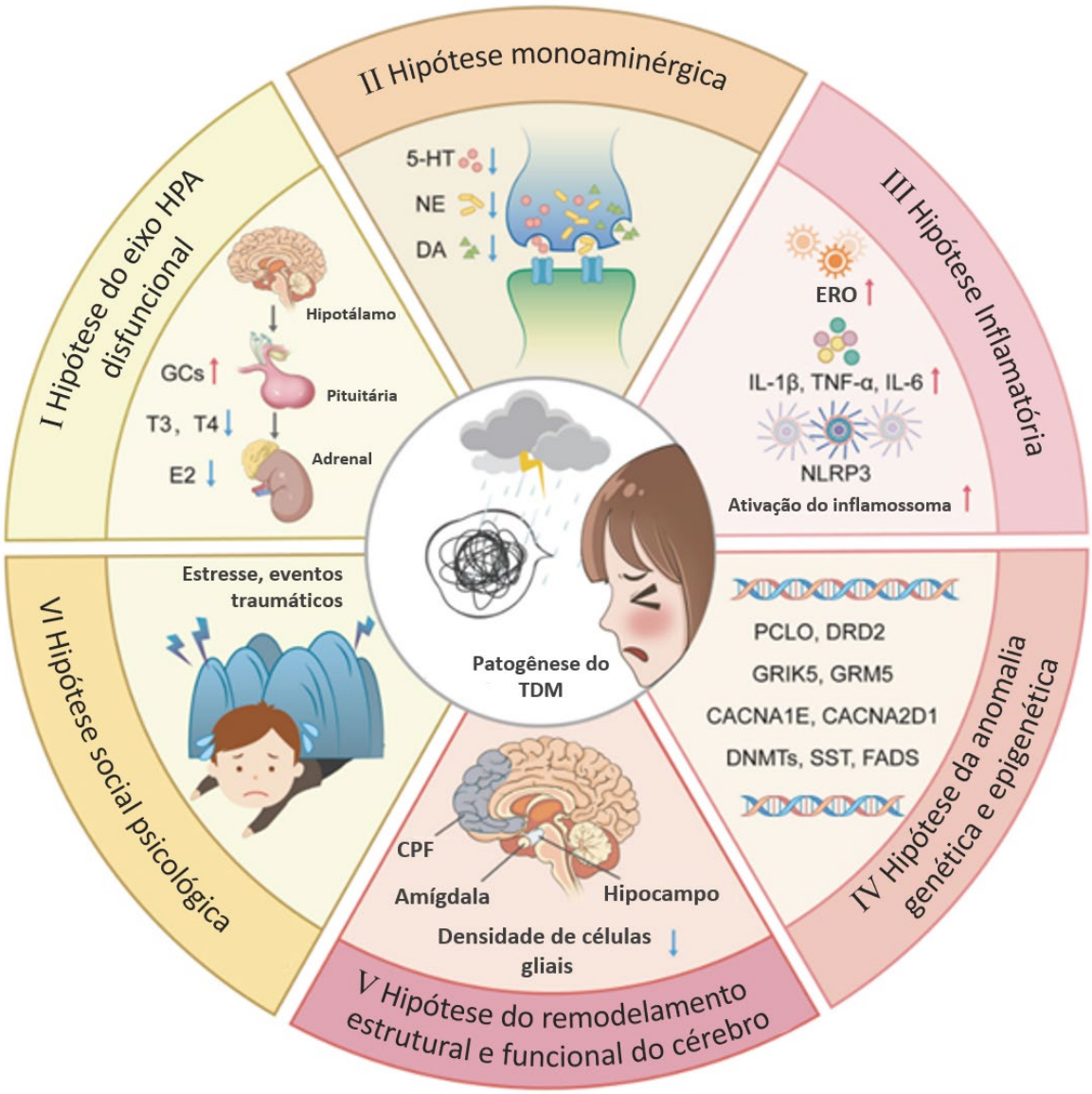

Figura 1. Principais hipóteses acerca da patologia do TDM, adaptado de Cui et al. (2024)

Níveis elevados de cortisol estão associados a características melancólicas, função cognitiva prejudicada, manifestações mais severas do transtorno depressivo, resposta clínica insatisfatória ao tratamento e recaídas, sendo que entre 64 e 73% dos indivíduos depressivos apresentam valores acima da média de cortisol quando comparados a um grupo saudável (Stetler and Miller, 2011). A combinação entre a liberação excessiva de cortisol relacionada ao estresse e a falha na inibição por retroalimentação mediada por receptores glicocorticoides se destacam como os principais prováveis mecanismos por trás da hipótese associada à

dessensibilização do eixo HPA (Malhi e Mann, 2018). Mais especificamente a exposição ao estresse desencadeia a síntese do hormônio liberador de corticotrofina (CRH) e da arginina vasopressina (AVP) no hipotálamo com destino a hipófise, que em decorrência desse estímulo, libera o hormônio adrenocorticotrófico (ACTH). Na glândula adrenal, o ACTH estimula a produção e liberação dos hormônios glicocorticoides na circulação, dentre eles o cortisol (Hantsoo et al., 2023).

Por outro lado, a deficiência de neurotransmissores como a serotonina (5-HT), dopamina (DA) e norepinefrina (NE), é destacada como a origem dos transtornos depressivos, de acordo com a hipótese monoaminérgica (Cui et al., 2024). Alguns medicamentos antidepressivos de primeira geração, como a classe dos inibidores da monoamina oxidase (IMAO), serviram de ponto de partida para pesquisas relacionadas a essa hipótese, justamente por conta de sua eficácia terapêutica como agente antidepressivo e seu mecanismo de ação, que leva ao aumento na concentração de serotonina e noriepinefrina na fenda sináptica (Schildkraut, 1965).

Estudos relacionam a diminuição da síntese de serotonina com o aumento do perfil inflamatório central. O aumento da produção de citocinas pró-inflamatórias se relaciona diretamente com a diminuição da atividade da triptofano hidroxilase e um aumento da atividade da indoleamina 2,3-dioxigenase (IDO). Dessa forma, a relação entre o fortalecimento do perfil inflamatório e a menor biodisponibilidade de serotonina tem ganhado atenção do mundo científico (Savitz, 2017)(Brown et al., 2021).

Múltiplos estudos investigam a correlação entre os marcadores pró-inflamatórios e o TDM, sendo que é observado um aumento nos níveis de Interleucina-6 (IL-6), fator de necrose tumoral alpha (TNF-α), Interleucina-1β (IL-1β) e proteína C reativa (PCR) em indivíduos depressivos (Pasco et al., 2010). Destaca-se também que a PCR, quando medida se utilizando um método de alta sensibilidade, apresenta uma correlação moderada com o desenvolvimento de TDM. O aumento na proteína C reativa de alta sensibilidade (ln-hsPCR) aumenta a razão de risco para o desenvolvimento de TDM em 44% (Milaneschi et al., 2020).

Apesar desta correlação entre os marcadores inflamatórios e o transtorno depressivo, o mecanismo por trás dessa interação ainda não está completamente elucidado. Sabe-se que gordura corporal excessiva acarreta um aumento sérico de PCR e pode ser considerado um marcador de inflamação leve, visto que o tecido adiposo apresenta a capacidade de produção de IL-6 e TNF-α, além de regular outras citocinas (Yudkin et al., 1999). Estudos realizados em modelos animais também apontam para uma importante relação do comportamento tipo

depressivo com o dano isquêmico, estresse oxidativo e exposição a lipopolissacarídeos (LPS), sendo que os dois primeiros desencadeiam um aumento na produção de espécies reativas de oxigênio que, por sua vez, levam a um aumento de interferon-gama (IFN-γ), TNF-α, IL-6, IL-1β e de Óxido Nítrico Sintase Induzível (iNOS), enquanto os LPS promovem um aumento destes marcadores através da via TLR-4 (Receptor toll-like 4) e da ativação dos fatores de transcrição NF-kB (Fator nuclear Kappa B) e AP-1 (proteína ativadora-1) (Cui et al., 2024).

Em outro aspecto, ao se analisar o componente genético do TDM, destaca-se primeiramente sua hereditariedade, que varia entre 30 e 50% (Kendall et al., 2021). Adicionalmente, Lohoff (2010) descreve alguns genes candidatos para a susceptibilidade ao TDM, como o gene do transportador de serotonina (5HTT/SLC6A4) e o gene do receptor de serotonina 2A (HTR2A), ambos despertando interesse por conta da hipótese monoaminérgica e de seu papel como alvos terapêuticos para medicamentos antidepressivos. Além desses, destaca-se também os genes do BDNF e da triptofano hidroxilase (TPH2), por conta de sua participação no estímulo para a neurogênese e síntese de serotonina, respectivamente. Por fim, Lohoff salientou que os estudos de associação do genoma completo (GWAS), até então, apresentaram essencialmente resultados negativos, e que seriam necessárias análises combinadas muito maiores de casos e controles para que fosse possível identificar genes estatisticamente significantes.

Em concordância, Levinson et al. (2014) calcula que para produzir resultados significantes com GWAS seria necessário um N superior a 75,000-100,000 de casos. Dessa forma, em um GWAS realizado por Hyde et al. (2016), utilizando dois conjuntos, o primeiro contendo 75,607 indivíduos com diagnóstico de depressão declarado e 231,747 controles, que reportaram nunca terem recebido um diagnóstico de depressão, e o segundo, independente do primeiro e com o objetivo de validação, apresentando 45,773 casos e 106,354 controles, identificaram ao todo 15 loci gênicos com significância ($p\text{-val} < 5\times10^{-8}$). Desde então, diversos estudos com metodologia semelhante e populações amostrais cada vez maiores foram realizados, sendo que utilizando análises combinadas para formar um conjunto contendo mais de 1,2 milhões de indivíduos, 178 loci de risco já foram identificados (Levey et al., 2021).

Fatores ambientais, como a exposição ao estresse, também contribuem significantemente para o desenvolvimento do TDM, tanto de forma independente, como em conjunto com fatores genéticos (Kendall et al., 2021). Situações traumáticas ou estressantes apresentam grande potencial para a manifestação de um episódio depressivo maior, com destaque para o potencial de indução do transtorno associado à perda de emprego, casos

extraconjugais e divórcio (Slavich and Sacher, 2019), sendo que de maneira geral eventos adversos na vida são capazes de levar ao desenvolvimento do TDM (Monroe and Harkness, 2022). Alterações estruturais no encéfalo de indivíduos depressivos também já foram documentadas, como anormalidades na estrutura cortical de diversas regiões, com destaque para a porção medial do córtex orbitofrontal, com alterações registradas consistentemente em múltiplas análises envolvendo adultos, adolescentes e correlações clínicas (Schmaal et al., 2017). Adicionalmente, o volume do hipocampo (Schmaal et al., 2016) e do giro denteado também se mostram reduzidos em indivíduos depressivos (Boldrini et al., 2013)(Boldrini et al., 2018).

No aspecto funcional, as redes cerebrais envolvidas em processos chave da regulação emocional, quando avaliadas através da neuroimagem, demonstraram que a amígdala apresenta conectividade e atividade aumentadas. O córtex cingulado anterior apresenta hiperatividade e a insula e córtex pré-frontal dorsolateral se encontram hipoativos (Hamilton et al., 2012) (Pizzagalli, 2014). Entretanto, tais dados têm se mostrado difíceis de replicar (Müller et al., 2017).

2.3 PERSPECTIVAS DE TRATAMENTO E REMISSÃO

Convencionalmente, as estratégias terapêuticas para o TDM se concentram em farmacoterapia e psicoterapia, com destaque para as classes dos antidepressivos tricíclicos (ADTs), inibidores seletivos de recaptação da serotonina (ISRS) e inibidores seletivos de recaptação da serotonina e adrenalina (ISRSN) (Cui et al., 2024). Entretanto, em vista do número significativo de pacientes que apresentam o transtorno depressivo resistente, ou seja, que não respondem ao tratamento mesmo após a administração de pelo menos 2 medicamentos distintos; destaca-se a necessidade de investigação acerca de estratégias antidepressivas alternativas (Swainson et al., 2019). Além da combinação de múltiplos antidepressivos e uso de agentes adjuvantes, uma das estratégias emergentes é a utilização de cetamina e do seu enantiômero a escetamina, que diferentemente dos ISRS, atuam como antagonistas do glutamato (GLU), tendo um alvo primário distinto e apresentando potencial de eficácia mesmo em indivíduos que se mostraram resistentes a outras drogas (Ruberto et al., 2020).

Os resultados do tratamento de TDM são apresentados na literatura de duas formas principais: a primeira, com maior foco na eficácia e na investigação do potencial terapêutico dos medicamentos, e que utiliza a redução dos sintomas em 50% como medida de sucesso

(Keller, 1992) e a segunda, que busca a remissão completa dos sintomas, uma medida mais próxima do objetivo clínico do tratamento (Malhi and Mann, 2018). Os sintomas depressivos normalmente são descritos através de escalas avaliativas, como a *hamilton depression rating scale* (HDRS), presente em duas versões, uma com 17 e a outra com 21 itens (Hamilton, 1960) (Hamilton, 1967) que fazem uma aproximação semiquantitativa da intensidade dos sintomas presentes em um determinado indivíduo.

Ao se avaliar as perspectivas de tratamento no TDM, os resultados se mostram insatisfatórios. Mais de 50% dos pacientes não alcançam a remissão completa dos sintomas mesmo após 6 semanas de tratamento, e apenas 67% chegam à remissão após 4 cursos de tratamento utilizando múltiplos medicamentos, como relatado pelo estudo de larga escala STAR*D (Alternativas de Tratamento Sequenciado para Aliviar a Depressão), contendo mais de 4 mil pacientes (Rush et al., 2006).

Mais recentemente, em uma metanálise reunindo mais de 110 mil pacientes, foi avaliada a eficácia dos principais medicamentos antidepressivos. Esse estudo mostrou que apesar de todos os 21 medicamentos se mostrarem significantemente mais eficazes do que o placebo no tratamento da depressão (com destaque para a amitriptilina e mirtazapina), somente dois, a agomelatina com uma taxa de abandono de 0,84 (0,72 a 0,97) em comparação ao placebo e a fluoxetina 0,88 (0,80 a 0,96), apresentaram aceitabilidade significante. Ainda, destaca-se nesse trabalho a dificuldade de adesão aos protocolos de tratamento (Cipriani et al., 2018), muito por conta dos seus efeitos colaterais, visto que alguns dos mais eficazes, como os ADTs e IMAOs, estão entre os fármacos menos utilizados no tratamento do TDM (Undurraga and Baldessarini, 2017).

2.4 EIXO HPA E NERVO VAGO

A interação bidirecional entre o ecossistema presente no intestino e o sistema nervoso, responsável pelo eixo microbiota-intestino-cérebro, é baseada em vias metabólicas, endócrinas, neurais e imunológicas, incluindo o nervo vago, o eixo HPA, mediadores imunológicos, a produção de metabólitos bacterianos e a sinalização enteroendócrina (Góralczyk-Bińkowska et al., 2022).

A porção imune dessa regulação se dá principalmente através de alterações na secreção de citocinas, enquanto o sistema nervoso participa principalmente através de impulsos que percorrem o sistema nervoso autônomo (SNA), incluindo o nervo vago, fibras aferentes, eferentes e o sistema nervoso entérico (SNE) (Gershon, 1998), uma complexa rede de neurônios

e células da glia, que utiliza mais de 30 neurotransmissores e se assemelha ao sistema nervoso central (SNC) tanto estruturalmente como funcionalmente, sendo chamado também de “o segundo cérebro” (Gershon, 1999).

As fibras eferentes do nervo vago, que encaminham os sinais do SNC para o SNE, correspondem a 10-20% de todas as fibras, enquanto as fibras aferentes, envolvidas na ativação/regulação do eixo HPA, constituem os 80-90% restantes, indicando uma maior intensidade na comunicação de sentido entérico-central, o que é corroborado pelo fato de que mesmo após uma vagotomia os intestinos retêm a sua capacidade funcional (Breit et al., 2018). Adicionalmente, o cortisol, um dos produtos da ativação do eixo HPA (Hantsoo et al., 2023), além de influenciar as células do sistema imune e modular a secreção de citocinas que atuam no próprio eixo HPA, também interfere significantemente no funcionamento e diferenciação da microbiota intestinal (Foster et al., 2021).

2.5 VIAS NEUROENDÓCRINAS E BARREIRA HEMATOENCEFÁLICA

Além da caracterização do SNE inicialmente descrita por Gershon (1998), e que já discutia a função secretora de serotonina das células ECL, a literatura passou por atualizações, notavelmente, quando se observa a função das células tipo-*neuropod*, células sensoriais de caráter epitelial que possuem a capacidade de formar sinapses com neurônios aferentes do nervo vago. Estas células possuem no seu interior grandes vesículas densas contendo neuropeptídeos de função endócrina como colecistocinina (CCK), secretina e serotonina, além de vesículas menores contendo neurotransmissores, incluindo o glutamato. Uma vez estimuladas, estas células seriam capazes de realizar a transdução de sinal para diferentes propriedades dos estímulos entéricos, como valor nutricional, distensão mecânica, osmolaridade, pH ou temperatura, sendo capazes de disparar tanto sinais mais lentos (endócrinos), como rápidos (liberação de glutamato nas sinapses com o nervo vago) (Kaelberer et al., 2020).

Em contato com toda essa maquinaria celular, a microbiota apresenta uma significante interação com o macroorganismo por diferentes vias, produzindo precursores de neurotransmissores, catalisando a síntese desses neurotransmissores através do metabolismo dietético ou ambos. Como exemplo, alguns metabólitos produzidos por certos táxons de bactérias esporulantes atuam como moléculas sinalizadoras na promoção da síntese e liberação de serotonina nas células tipo-enterocromafim (Yijing Chen et al., 2021).

Mais especificamente, substâncias envolvidas na comunicação da própria comunidade microbiana intestinal também apresentam efeitos sistêmicos e periféricos no organismo, que afetam o funcionamento cerebral, como a produção do ácido gama-aminobutírico (GABA) *Lactobacillus* spp. e *Bifidobacterium* spp., acetilcolina por *Lactobacillus* spp. Serotonina por *Escherichia* spp., *Candida* spp. e *Enterococcus* spp., dopamina por *Bacillus* spp. e noradrenalina por *Bacillus* spp. e *Saccharomyces* spp. (Dinan et al., 2014).

2.6 MECANISMOS IMUNOLÓGICOS E INFLAMAÇÃO

Observa-se uma correlação significativa entre o processo inflamatório e os transtornos mentais, incluindo o TDM (Jones et al., 2020). A síndrome do intestino permeável, caracterizada pela elevada permeabilidade intestinal em decorrência de uma barreira epitelial intestinal disfuncional, é um importante fator no quadro inflamatório de múltiplas patologias, como pancreatite aguda, doença renal crônica, síndrome do intestino irritável e depressão (Fukui, 2016). Citocinas pró inflamatórias como a IL-6, IL-1β e IFN-γ, ativam a IDO, que por sua vez direciona o metabolismo do triptofano para a via da KYN, reduzindo a sua disponibilidade para a síntese de serotonina e potencialmente elevando a concentração de metabólitos neurotóxicos como o ácido quinolínico (QUIN) (Cryan and Dinan, 2012) (Paul et al., 2022).

Estudos recentes demonstram que o estresse oxidativo, desempenha um papel crucial na neuroinflamação e na disfunção neuronal associadas ao TDM. Biomoléculas pertencentes às vias de estresse oxidativo e nitrosativo, como a superóxido dismutase (SOD1), Malondialdeído (MDA) e metabólitos do óxido nítrico (NOx) se encontram significantemente elevados em indivíduos depressivos. Similarmente, produtos da oxidação de moléculas orgânicas como hidroperóxidos de lipídios (LOOH) e produtos proteicos de oxidação avançada (AOPP) estão positivamente associados aos escores de sintomas depressivos (Maes et al., 2019). As espécies reativas de oxigênio (ERO) também apresentam o potencial de elevar a concentração de citocinas pró inflamatórias, tal como a IL-1β, com capacidade de interferir no metabolismo do triptofano (Early et al., 2018).

Adicionalmente, os LPS, integrantes da membrana externa de bactérias gram negativas, atuam como um fator de virulência (Allen and Imperiali, 2019) e estão correlacionados com sintomas tipo depressivos em modelos animais. Wang et al. (2019) demonstraram que após administração de LPS, camundongos apresentaram comportamento tipo-depressivo, avaliado

através do teste de nado forçado, suspensão pela cauda e preferência por sacarose. Além disso, também foram constatados uma diminuição na expressão de BDNF e um aumento nos marcadores pró inflamatórios IL-1β e TNF-α.

2.7 METABOLISMO DO TRIPTOFANO, QUINURENINA E ÁCIDO QUINOLÍNICO

O triptofano (TRP) proveniente da dieta apresenta dois destinos principais ao interagir com o organismo. Menos de 5% é direcionado para a produção de serotonina e mais de 95% servem como precursor para a via da quinurenina (KYN) (Deng et al., 2021). Dentro dos possíveis destinos dessa via, representada pela figura 2, destacam-se o ácido quinurênico (KYNA), ácido picolínico (PIC) e a nicotinamida (NAM), associados a efeitos neuroprotetores e apresentando níveis séricos diminuídos no TDM, e o ácido quinolínico (QUIN), associado a neurotoxicidade quando em níveis elevados no TDM. Adicionalmente, a proporção de metabólitos neuroprotetores em relação aos neurotóxicos se mostra consistentemente diminuída na periferia em indivíduos com transtorno depressivo (Paul et al., 2022).

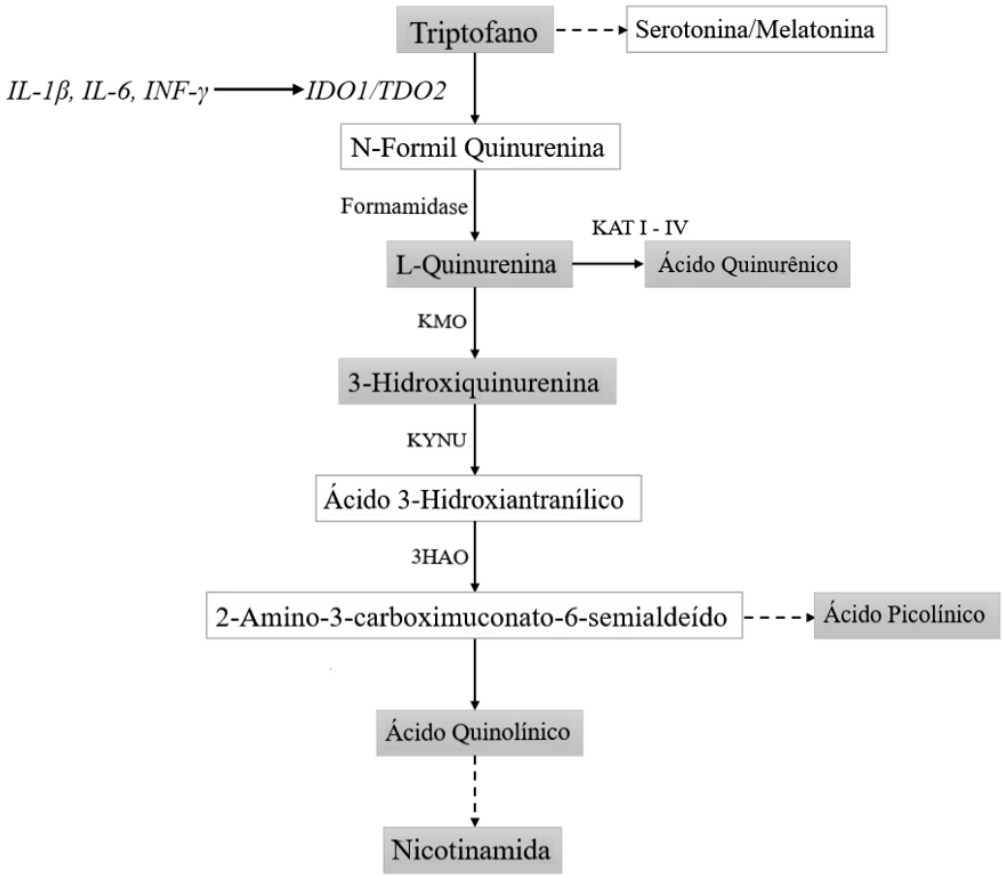

Figura 2. Via da quinurenina. IL: interleucina, INF: interferon, IDO1: indoleamina 2,3-dioxigenase 1, TDO2: triptofano-2,3-dioxigenase 2, KAT: quinurenina aminotransferase, KMO: quinurenina 3-monooxigenase, KYNU: quinureninase, 3HAO: ácido 3-hidroxi-antranílico. Adaptado de Paul et al., (2022)

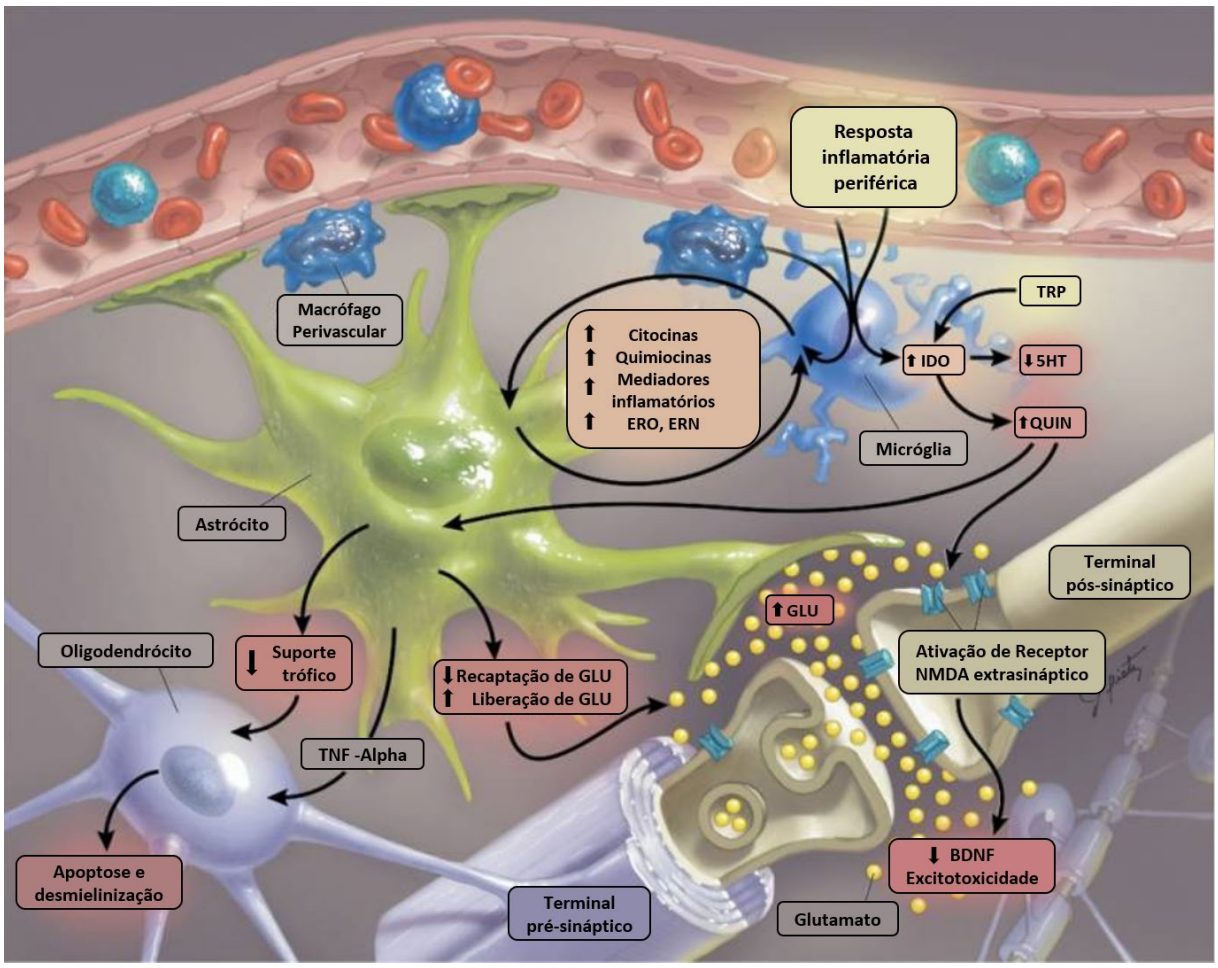

Figura 3. Efeitos da cascata inflamatória no SNC. 5-HT: serotonina; BDNF: fator neurotrófico derivado do cérebro; CNS: sistema nervoso central; GLU: glutamato; IDO: indoleamina 2,3-dioxigenase; IFN: interferon; IL: interleucina; NMDA: N-metil-D-aspartato; QUIN: ácido quinolínico; ERN: espécies reativas de nitrogênio; ERO: espécies reativas de oxigênio; TNF: fator de necrose tumoral; TRP: triptofano. Adaptado de (Miller et al., 2009)

Dentro desse contexto, além do perfil inflamatório, a microbiota intestinal também é capaz de afetar os níveis e o metabolismo do triptofano. Como exemplo pode-se citar a bactéria *Bifidobacterium infantis*, que promove o aumento dos níveis de triptofano no corpo, ou ainda certas bactérias esporulantes do gênero Clostridiales, que apresentam um importante papel no direcionamento do triptofano para a via da serotonina, visto que as células ECL, dentro das quais ocorre essa conversão, dependem dos ácidos graxos de cadeia curta sintetizados por essas bactérias dentro do intestino (Yijing Chen et al., 2021) (Góralczyk-Bińkowska et al., 2022).

2.8 PRINCIPAIS FATORES DE INFLUÊNCIA NA MICROBIOTA

Naturalmente, assim como a microbiota apresenta a capacidade de influenciar em diversos aspectos da saúde de seu hospedeiro, ela mesmo pode ser influenciada. Dentro dos múltiplos elementos que exercem influência sobre a composição e abundância da microbiota intestinal, a dieta se destaca como um fator chave (Gubert et al., 2020). Nutrientes provenientes da alimentação como vitaminas, minerais, ácidos graxos poli-insaturados e aminoácidos se mostram cruciais na manutenção da estrutura e funcionamento cerebral. Eles atuam como cofatores em centenas de diferentes enzimas, contribuem em diversas vias metabólicas, na sinalização celular, síntese de neurotransmissores, manutenção da bainha de mielina, metabolismo de lipídios e glicose, função mitocondrial e prevenção de oxidação (Parletta et al., 2019).

Outro fator de destaque é o parto, que representa o momento do primeiro contato entre o recém-nascido (RN) e o ambiente, sendo crítico no processo de colonização do trato gastrointestinal (Linehan et al., 2022). A Microbiota de RN de parto normal se assemelha à microbiota vaginal mãe, com destaque para *Lactobacillus dominates*, *Senathia* spp. e *Prevotella*, com a maior parte sendo de caráter anaeróbio. Em contraste, o procedimento de cesariana leva a um desequilíbrio na microbiota intestinal infantil e diversidade reduzida, já que o primeiro contato do RN é com a pele da mãe e o ambiente hospitalar. Como consequência,

patógenos hospitalares já foram encontrados no trato gastrointestinal destes RN (Shao et al., 2019).

Neonatos provenientes de cesariana apresentam uma microbiota intestinal com menor abundância de *Bacteroides*, *Staphylococcus*, *Bifidobacteria*, *Corynebacterium* e *Propionibacterium*, enquanto *Lactobacillus*, *Prevotella*, *Sneathia* spp., e *Clostridioides difficile* se encontram aumentados, sendo que uma elevada abundância de *Clostridioides difficile* poderia causar um quadro de disbiose e trazer risco aumentado para o desenvolvimento de obesidade (Kumar et al., 2016).

Entretanto, o parto pode não ser o primeiro contato com microrganismos, visto que amostras de mecônio e fluído amniótico positivas para a presença de DNA (ácido desoxirribonucleico) microbiano já foram sequenciadas. Este estudo, realizado em grávidas com ausência de infecção uterina e que passaram por uma cesariana, indica que este processo de colonização já teria início na vida intrauterina (Stinson et al., 2019). Ainda, ao longo da vida, múltiplos fatores externos são capazes de influenciar na composição da microbiota intestinal, sendo os principais: estilo de vida e dieta, seguidos por genética do hospedeiro e localização geográfica (Parizadeh and Arrieta, 2023).

2.9 TDM E MICROBIOTA INTESTINAL: QUAL A RELAÇÃO?

Existe uma quantidade de dados cada vez maior estabelecendo uma conexão entre a microbiota intestinal e o desenvolvimento e funcionamento do sistema nervoso central, caracterizando um sistema de comunicação bidirecional associado à homeostase intestinal, mas também à motivação e às funções cognitivas superiores. Este sistema é denominado de eixo microbiota-intestino-cérebro, ou simplesmente intestino-cérebro. Nos últimos anos, principalmente a partir de estudos em modelos animais, se observou uma ligação entre a composição da microbiota intestinal e transtornos mentais (Gulas et al., 2018).

Um componente chave deste eixo é justamente a microbiota, caracterizada pelo conjunto de microrganismos que colonizam o corpo humano, nessa relação denominado também de macroorganismo. Por outro lado, o termo microbioma agrega os genomas de todos esses microrganismos dispostos neste ambiente. As interações que ocorrem entre os múltiplos agentes desse complexo ecossistema formam uma rede de interrelações tanto positivas, como negativas, capaz de influenciar significantemente a saúde do hospedeiro (Rinninella et al., 2019).

Apesar de estarem presentes em múltiplas regiões do organismo, as maiores e mais complexas populações de microrganismos se encontram no trato gastrointestinal, constantemente se adaptando ao seu ambiente e participando em funções críticas do hospedeiro, como regulação da imunidade, obtenção de energia dos alimentos e prevenindo a colonização por patógenos (Singh et al., 2021). Além disso, a microbiota intestinal também desempenha um importante papel na neutralização de toxinas e componentes carcinogênicos (Claus et al., 2016). Ademais, através da fermentação anaeróbia de carboidratos não digeríveis, produzem ácidos graxos de cadeia curta (AGCC), que servem de fonte de energia primária para as células epiteliais do cólon, os colonócitos (Silva et al., 2020).

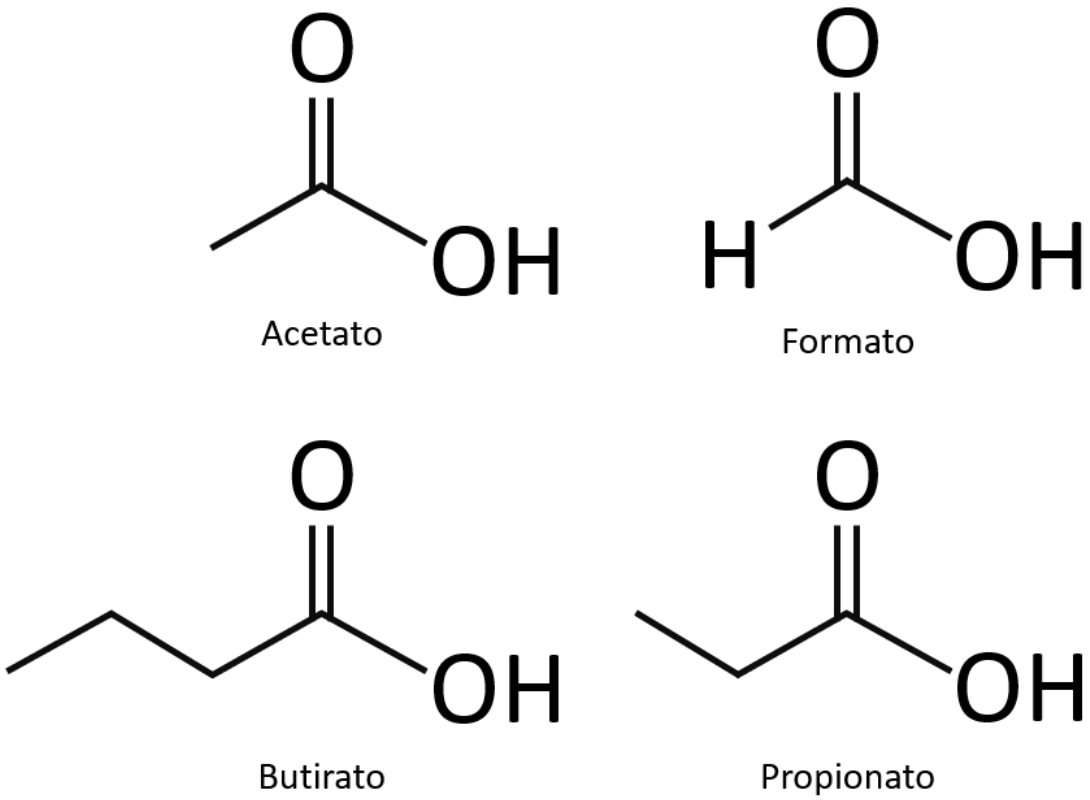

Figura 4. Principais AGCC provenientes da fermentação de frutooligossacarídeos. Fonte: O Autor

Diferentes bactérias apresentam a capacidade de produzir AGCC, como: *Clostridium spp., Eubacterium spp., Fusobacterium spp., Butyrivibrio spp., Megasphaera elsdenii, Mitsuokella multiacida, Roseburia intestinalis, Faecalibacterium prausnitzii, e Eubacterium halli* (Mirzaei et al., 2021). Além de seu papel como fonte de energia para os enterócitos, os AGCC também atuam na modulação do metabolismo de lipídios e homeostase da glicose, aumentam a sensibilidade a glicose, elevam a eficiência e função mitocondrial, contribuem para regulação do peso corporal, redução do apetite e no controle da inflamação (Bourassa et al., 2016).

Assim, a sobreposição entre as hipóteses de desenvolvimento do TDM, e as vias de interação da microbiota com o organismo humano, justifica uma investigação acerca das alterações na composição da microbiota intestinal em indivíduos com TDM.

3 OBJETIVOS

3.1 OBJETIVO GERAL

Realizar uma revisão sistemática da literatura para analisar a diversidade alfa e beta e a abundância relativa de microrganismos na microbiota intestinal de indivíduos diagnosticados com TDM, identificando possíveis associações entre a composição microbiana e a depressão.

3.2 OBJETIVOS ESPECÍFICOS**:**

1. Investigar como a diversidade alfa (variedade dentro de uma amostra) e beta (diferença entre amostras) da microbiota intestinal varia entre indivíduos com transtorno depressivo maior e indivíduos saudáveis.
2. Identificar quais filos, ordens, famílias e gêneros de microrganismos apresentam maior ou menor abundância relativa na microbiota intestinal de indivíduos com TDM em comparação com controles saudáveis.
3. Analisar se há diferenças consistentes na composição microbiana intestinal em diferentes estudos e populações, e discutir as associações relatadas entre microbiota e transtorno depressivo maior.
4. Explorar as possíveis implicações da diversidade microbiana intestinal e da abundância relativa de certos microrganismos para a compreensão da fisiopatologia do transtorno depressivo maior, considerando mecanismos biológicos sugeridos na literatura.

4 RESULTADOS E DISCUSSÃO

Os resultados deste trabalho estão apresentados na forma de artigo científico. O artigo entitulado “Alterations in Gut Microbiota Composition in Major Depressive Disorder: A Systematic Review” está, em sua integridade, descrito a seguir, sendo que sua formatação segue os moldes do periódico ***Psychiatry Research***, onde foi submetido.

Alterations in Gut Microbiota Composition in Major Depressive Disorder: A Systematic Review

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Abstract: A growing body of data establishes a connection between the gut microbiota and the development and functioning of the central nervous system, pointing to a bidirectional communication system associated not only with intestinal homeostasis but also with certain mental disorders, such as major depressive disorder (MDD). In this systematic review, we consolidate information from the current literature regarding the composition of the gut microbiota in individuals with MDD compared to healthy controls, focusing on measures of alpha and beta diversity, as well as the phyla, orders, families, and genera that are differentially abundant between these groups. Twenty-nine studies were identified, encompassing 1,352 patients with MDD and 1,284 control individuals. Our investigation suggests no consistent differences in alpha diversity (both in terms of richness and evenness) between the MDD and healthy controls. In contrast, beta diversity results appear to distinguish between these groups more reliably. Additionally, we found that certain microbial taxa were consistently less abundant in the MDD population. These taxa included groups that could synthesize short-chain fatty acids (SCFAs), with anti-inflammatory potential, and associated with reducing toxic kynurenine metabolites. Conversely, taxa associated with pro-inflammatory characteristics, IDO enzyme activation, and directing tryptophan metabolism towards the synthesis of neurotoxic kynurenine metabolites, were more abundant in the MDD group than in healthy controls.

Keywords: Major depressive disorder, Gut microbiota, Relative abundance, Inflammation, Kynurenine, Short chain fatty acids, neurotoxicity.

1. Introduction

The World Health Organization (WHO) points out that 3.8% of the world's population suffers from a depressive disorder; in adults, this figure corresponds to 5% (4% of men and 6% of women). In all, 280 million people are affected, and more than 700,000 deaths are recorded annually as a result of suicide, a cause of death that ranks fourth among the most frequent in the 15-29 age group (World Health Organization, 2023).

In addition, when evaluating disability-adjusted life years (DALYs), major depressive disorder (MDD) manifests itself as the most disabling disease in the Americas (Swainson et al., 2019a). In Brazil, schizophrenia and common psychiatric disorders are responsible for more than 150,000 hospitalizations per year, which corresponds to an average annual expenditure of US$ 67,216,056 on hospital expenses (Carteri et al., 2020).

The pathology of MDD is known to be associated with multiple factors that are commonly grouped into different hypotheses, although they often interact with each other. The monoaminergic, inflammatory, genetic and epigenetic, structural and functional remodeling of the brain, social psychological and dysfunctional HPA axis hypotheses encompass most of these factors (Cui et al., 2024a).

However, an increasing amount of data establishes a connection between the gut microbiota and the development and functioning of the central nervous system, characterizing a bidirectional communication system associated with intestinal homeostasis, motivation, and higher cognitive functions. This system is called the microbiota-intestine-brain axis, or simply gut-brain axis. In recent years, mainly from studies in animal models, a link has been observed between the composition of the gut microbiota and mental disorders (Gulas et al., 2018).

Several authors have tried to associate alterations in the taxa present in the gut microbiota with the pathophysiology of MDD. Tools for assessing the global diversity of microorganisms, such as alpha diversity alone, have shown unsatisfactory results regarding their ability to distinguish between individuals with MDD and healthy controls (Sanada et al., 2020). Beta diversity appears to be more promising in differentiating between individuals with and without MDD. Thus, the association between these tools and relative abundance measures has become increasingly frequent (Gao et al., 2023b)(McGuinness et al., 2022).

The bidirectional interaction between the gut ecosystem and the nervous system, responsible for the microbiota-intestine-brain axis, is based on metabolic, endocrine, neural, and immunological pathways, including the vagus nerve, the HPA axis, immunological mediators, the production of bacterial metabolites and enteroendocrine signaling(Góralczyk-Bińkowska et al., 2022). As an example, some metabolites produced by certain taxa of sporulating bacteria act as signaling molecules in promoting the synthesis and release of serotonin in enterochromaffin-like cells (ECL) (Yijing Chen et al., 2021)

More specifically, substances involved in the communication of the intestinal microbial community itself also have systemic and peripheral effects on the body, capable of affecting brain function, such as the production of gamma-aminobutyric acid (GABA) *by Lactobacillus* spp. and *Bifidobacterium* spp, acetylcholine by *Lactobacillus* spp. serotonin by *Escherichia* spp., *Candida* spp. and *Enterococcus* spp. dopamine by *Bacillus* spp. and noradrenaline by *Bacillus* spp. and *Saccharomyces* spp. (Dinan et al., 2014).

Changes in the composition of the gut microbiota, such as an increase in *Enterobacteriaceae* and *Eggerthela* and a decrease in *Faecalibacterium*, may be associated with a heightened systemic inflammatory profile, with an increase in IL-6, TNF-alpha and other inflammatory markers important in the pathophysiology of MDD (Zeng et al., 2016; Sokol et al., 2008; Forbes et al., 2018). Systemic inflammation and neurotoxic kynurenine metabolites are associated with decreased BDNF and neurogenesis and activation of signaling pathways involved in apoptosis in MDD (Stetler and Miller, 2011). In contrast, an increase in *Roseburia* is associated with a reduction in systemic and central inflammation (Nie et al., 2021) and a reduction in toxic metabolites from the kynurenine pathway, such as quinolinic acid (Zhou et al., 2023). These results, taken together, may indicate a path to be followed in the investigation of changes in the intestinal microbiota and their possible beneficial effects on the functioning of the central nervous system in MDD.

Therefore, in this systematic review, we condensed information from the current literature on the composition of the gut microbiota of individuals with major depressive disorder compared to healthy controls, focusing on the phyla, orders, families, and genera that are differentially abundant between these groups, as well as on measures of alpha and beta diversity.

2. Methodology

2.1. Search strategy

The search was carried out without restrictions on language or year of publication. The studies were selected from a search on October 2023 in the following databases: PubMed, EMBASE, Web of Science, and PsycINFO. The reference lists of all the studies included were examined to identify other eligible studies. We carried out manual searches of documents citing any of the studies initially included in our review, as well as studies included in previous systematic reviews. For the search in the databases, we used the following search terms: Depressive Disorders OR Depressive Syndrome OR Depression OR Depressive Symptoms AND Gastrointestinal Microbiome OR Gut Microbiome OR Gastrointestinal Microbiota OR Gastric Microbiome OR Intestinal Microbiome OR Brain-Gut.

The screening process was divided into three stages. In the first stage, duplicate studies were eliminated by manual review using Rayyan® software. In the second stage, the titles and abstracts were read by four pairs of reviewers, and studies that did not meet the eligibility criteria and were rejected by both reviewers were excluded. In the event of disagreement between the members of each pair, a third reviewer made the final decision. Finally, all the remaining relevant studies were assessed by reading the full text. For the studies included in the review, the list of references was reviewed, and potentially relevant studies were assessed for eligibility to ensure that all studies that met the inclusion criteria were included. The study selection process is represented in figure 1.

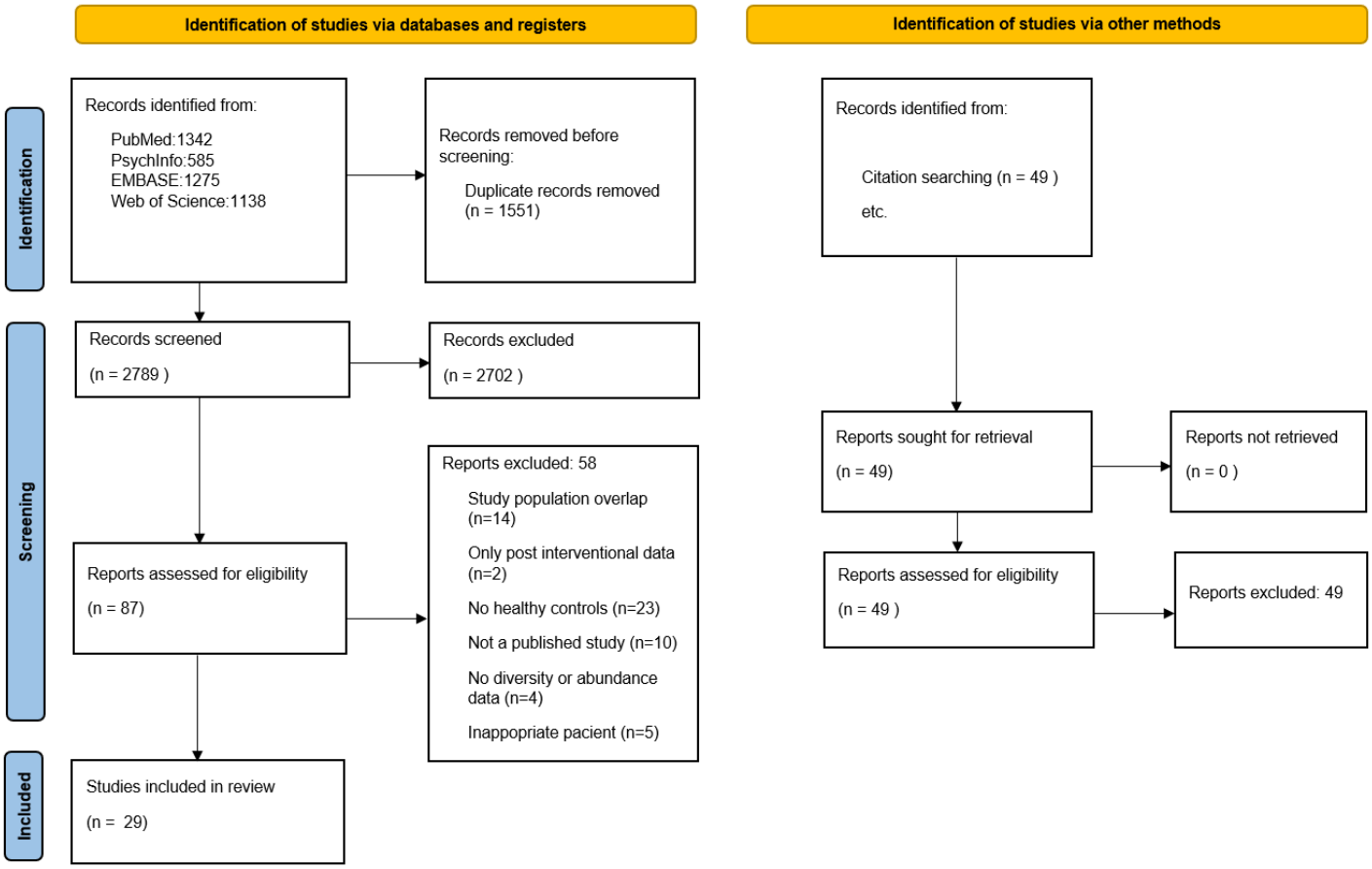

Fig. 1. PRISMA flowchart for the inclusion of studies.

For data collection, the following information was extracted: (1) the authors and date of the study; (2) population (i.e., number of subjects and their characteristics); (3) study design, (4) methods for sequencing and identifying the gut microbiota; (5) gut microbiota outcome data (alpha and beta diversity, taxonomic findings at the phylum, family and genus levels). As primary outcomes, we extracted measures of gut microbiota composition at the community level (alpha and beta diversity) and taxonomic findings at the phylum, family, and genus levels (relative abundance).

2.2. Eligibility criteria

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The research question was developed using the PECOS (Patient, Exposure, Comparators, Outcome, Study Design) strategy. Studies were considered eligible if they (1) sampled an adult population over the age of 18; (2) diagnosed subjects with unipolar depression; (3) compared subjects without the

disease/control; (4) performed gut microbiota analysis, diversity and abundance measures; (5) only observational studies; and (6) interventional studies containing a pre-intervention sample for the placebo/control and depressive groups. Systematic reviews, book chapters, reviews, theses/dissertations, and studies that featured patients diagnosed with depression associated with other psychiatric disorders and chronic inflammatory diseases were excluded from this systematic review.

2.3. Quality assessment

The quality assessment tool for cross-sectional and cohort observational studies and the quality assessment tool for controlled intervention studies from the US National Institutes of Health (NIH) Lung and Blood Institute were used to assess the quality of the included studies. To determine the quality of the studies, two authors (V.F. and M.M.) classified the included studies as "Good," "Fair," and "Poor." Classification disagreements were resolved with the participation of a third author, R.C. Body mass index (BMI), diet, and antidepressant or psychotropic medication were the key confounding variables for the quality assessment (National Institutes of Health, 2014).

3. Results

A search of four different databases identified 4340 records (PubMed:1342, PsychInfo:585, EMBASE:1275, Web of Science:1138). After manually removing duplicates using Rayyan® software, the remaining 2789 studies were evaluated in terms of their title and abstract, resulting in 87 being selected for full reading. Of these 87, 29 studies met all the requirements and were included in this systematic review. In addition, a search was carried out of the references of the included studies, which, despite generating 49 records for evaluation, did not result in any additional inclusions. The full list of included studies and their general characteristics can be seen in Table 1.

Authors	Design	Country	N Depressive group sample (Years; M/F)	N Control group sample (Years; M/F)	Severity scale(s)	Measured outcome	Genetic Analysis
Bai et al, 2022	Transversal	China	56 (35.7±15.9; 20/36)	56 (35.1±16.8;18/38)	HAMD	Fecal Microbiota Serum Biochemical Markers	16S rRNA gene sequencing using Illumina MiSeq platform Region: V3-V4 Database: RDP
Caso JR, et al. 2021	Transversal	Spain	Acute MDD: 46; 10/36 Remission MDD: 22; 5/17	45 (44.72; 11/34)	HAMD; EQ-Vas; PSS; LTE-Q; CTQ-SF total	Fecal Microbiota; Serum Biochemical Markers; Peripheral Blood Mononucleated Cells;	16S rRNA gene sequencing using Illumina MiSeq platform Region: V3-V4 Database: RDP
Chen HM, et al. 2022	Transversal	Taiwan	10 (40.9 ± 14.86; 2/8)	10 (38.2 ± 15.24; 3/7)	BDI; BAI; PSS	Fecal Microbiota; Fecal miRNAs	16S rRNA gene sequencing using Illumina Miseq and Region: V4 (MiniSeq) and V3-V4 (Miseq) Database: Greengenes v13.5
Chen JJ, et al. 2020	Transversal	China	Youngs: 25 (24.0±3.74; 7/18) Middle aged: 45 (44.96±7.76; 14/31)	Youngs: 27 (24.96±2.31; 8/19) Middle aged: 44 (47.16±8.07;10/34)	HAMD	Fecal microbiota	16S rRNA gene sequencing using Roche 454 Region: V3-V5 Database: RDP
Chen MM, et al. 2023	Transversal	China	40 (20; 26/14)	42 (21; 28/14)	HAMD; GAD-7; HAMA; PHQ-15	Fecal microbiota	Metagenomic sequencing using Illumina HiSeq2500 Database: NBCI NR and KEGG
Chen Y, et al. 2021	Transversal	China	62 (39.58 ±12.66, 0/62)	46 (36.93 ±8.58, 0/46)	HAMD; HAMA; PANSS; GAF	Fecal microbiota	16S rRNA gene sequencing using Illumina MiSeq Region: V3-V4 Metagenomic sequencing using Illumina NovaSeq 6000 platform Database: RDP, KEGG

Chen Z, et al. 2018	Transversal	China	10 (43.9±13.8; 5/5)	10 (39.6±9; 5/5)	HAMDS	Fecal microbiota	Metaproteomic analysis: Phylogenetic analysis of peptides using Mascot and Scaffold v. 4.4.8 Database: KEGG
Chung YE, et al. 2019	Transversal	Taiwan	36 (45.83±14.08; 8/28)	37 (41.19±12.73; 14/23)	BDI; PSS; BAI	Fecal microbiota	16S rRNA gene sequencing using Illumina MiSeq (n=53), 16S rRNA gene sequencing using Illumina MiniSeq (n=20) Region: V3-V4 (Miseq) V4 (MiniSeq) Database: Greengenes
Dong Z, et al. 2021	Transversal	China	23 (30.04±5.90; 7/16)	10 (30.22±6.50; 4/6)	HAMD-24; HAMA	Fecal microbiota; Neuroendocrine hormones	16S rRNA gene sequencing using Illumina MiSeq Region: V3-V4 Database: SILVA
Fontana A, et al. 2020	Transversal	Italy	Treatment resistant:8 (58.8; 4/4) Treatment Responsive:19 (53.7; 5/14) untreated: 7 (57; 13/7)	20 (37.7; 13/7)	HAMD	Fecal microbiota	16S rRNA gene sequencing using Illumina MiSeq Region: V3-V4 Database: Customized database based on NCBI.
Gao M, et al, 2023	Intervention	China	25 Treatment Resistant (24.40 ± 8.26; 16/9) 37 Responder (20.67 ± 6.35; 8/29)	32 (23.34 ± 3.13; 17/15)	HAMD	Fecal microbiota	16S rRNA gene sequencing using Illumina MiSeq PE300 platform. Region: V3-V4 Database: Greengenes
Han K, et al, 2023	Cohort	China	51 (27.14±8.98; 14/37)	30 (29.23±6.57; 10/20)	HAMD-24	Fecal microbiota	16S rRNA gene sequencing using the Illumina MiSeq Region:V3-V4 Database: SILVA
Jiang H, et al; 2015	Transversal	China	Active-MDD: 29 (25.3 ±5.4; 18/11) Responsed-MDD: 17 (27.1 ±5.4; 9/8)	30 (26.8 ±5.4; 15/15)	HAMD MADRS	Fecal microbiota serum cytokines Serum BDNF	16S rRNA gene sequencing using Roche 454 sequencing system Region: V1-V3 Database: RDP

Kovtun AS, et al. 2022	Transversal	Russia	36 (30 +/- 35; 19/17)	38 (34 +/- 36 ; 19/19)	HAMD-17 CES-D GAD-7	Fecal microbiota	Metagenomic sequencing on Illumina HiSeq X Ten. Database: NCBI RefSeq
Lai W, et al. 2019	Transversal	China	26 (43.73 ±11.46; 8/18)	29 (39.41 ± 10.96; 13/16)	HCL-32 HAMD HAMA	Fecal microbiota Microbial TRP	Metagenomic sequencing using Illumina Hiseq2500 sequencer Database: KEGG
Li X, et al. 2022	Transversal	China	40 (37,9 +/- 14.3; 15/25	22 (44 +/- 14.3; 13/ 9)	HAMD	Fecal microbiota	16S rRNA gene sequencing using Illumina MiSeq Region: V3-V4 Database: Greengenes
Lin P, et al. 2023	Cohort	China	50(ND;14/36)	60(ND;29/31)	HAMD	Fecal microbiota; Plasma IDO; KYN; and TRP	16S rRNA gene sequencing usingIllumina MiSeq platform Region V3-V4 Database: Silva (Release 132)
Liu P,et al. 2022	Transversal	China	66(24.20 ± 9.60;27/39)	43(23.67 ± 3.19;20/23)	HAMD-17; MINI	Fecal microbiota; Plasma inflammatory parameters	16S rRNA gene sequencing usingIllumina Novaseq PE250 Region V3-V4 Database: SILVA 132
Liu RT,et al. 2020	Transversal	USA	43(22.7±1.8;5/38)	47(21.7±2.1;13/34)	PROMIS; C-SSRS; SITBI	Fecal microbiota; Serum inflammatory cytokines;	16S rRNA gene sequencing using Illumina MiSeq Region: V4 Database: SILVA (132)
Maes M, et al (a). 2023	Transversal	Thailand	Major dysmood disorder: 12 (26.1 ± 10.6; 3/9) Simple dysmood disorder: 17 (26.5 ± 9.0; 3/14)	37 (28.4 ± 6.9; 6/31)	HAMD; BDI	Fecal microbiota	16S rRNA gene sequencing using MinION Mk1C Region: V1-V9 Database: RDP
Maes M, et al (b). 2023	Transversal	Thailand	32 (25.9 ± 9.1; 6/26)	37(28.4 ± 6.9;6/31)	HAMD; BDI	Fecal microbiota	16S rDNA gene sequencing using MinION Mk1C platform with R10.4 flow cell Region: V1-V9 Database: RDP

Rong H, et al. 2019	Transversal	China	31 (41.58 ± 10.40; 9/22)	30 (39.47 ± 10.22; 14/16)	MDQ; HCL-32 HAMD; HAMA	Fecal microbiota	Metagenomic sequencing using illumina HiSeq2500 Database: KEGG
Sun N, et al. 2022	Transversal	China	31(25.26±7.6;16/15)	29(24.79±4.92;13/16)	HAMD; HAMA	Fecal microbiota plasma bile acids	16S rRNA gene sequencing using Illumina MiSeq platform Region: V3-V4 Database: Greengenes
Tsai C, et al. 2022	Transversal	Taiwan	36 (65.6 ± 7.3; 8/28)	17 (64.1 ± 7.9; 8/9)	HAMD	Fecal microbiota Magnetic resonance imaging	16S rRNA gene sequencing using Illumina MiSeq platform Region V3-V4 Database: MetaSquare, Silva, Greengenes, RDP, HOMD,and Ezbiocloud
Yang J, et al. 2020	Transversal	China	Discovery set: 118 (27.19 ± 4.71; 51/67) Validation set: 38 (37.07 ± 9.45; 5/33)	Discovery set: 118 (26.86 ± 5.24; 51/67) Validation set: 37 (36.39 ± 10.75; 13/24)	HAMD; QIDS-16	Fecal microbiota; Fecal viruses; Fecal metabolites	Metagenomic sequencing using Illumina NovaSeq platform Database: NCBI NR
Ye X, et al. 2021	Intervention	China	26 (26.04 ± 7.83; 5/21)	28 (26.04 ± 7.83; 7/21)	HAMD	Fecal microbiota	16S rRNA gene sequencing using Illumina HiSeq 2500 platform Region: V3-V4 Database: RDP
Zhao H, et al. 2022	Transversal	China	24(29.96 ± 8.554;7/17)	26(31.31 ± 9.707; 8/18)	HAMD; HAMA IDS-SR30; QIDS-SR16	Fecal Microbiota Serum Biochemical Markers Magnetic resonance imaging	Metagenomic sequencing using Illumina Novaseq 6000 platform Database: NCBI NR
Zheng P, et al. 2020	Transversal	China	Discovery set: 122 (26.54 ± 4.07; 45/77) Validation set: 43 (37.13 ± 9.15; 14/29)	Discovery set: 171 (26.85 ± 5.48; 71/100) Validation set: 46 (45.4 ± 7.1; 24/22)	HAMD	Fecal microbiota	16S rRNA gene sequencing using Illumina MiSeq Region V3-V4 Database: RDP
Zheng S, et al. 2021	Transversal	China	30(30.80 ± 10.85; 12/18)	30(33.37 ± 7.02; 13/17)	HAMD	Fecal microbiota	16S rRNA gene sequencing using Illumina MiSeq Region V4-V5 Database:Not Informed

Table 1. Characteristics of included studies. Abbreviations: MDD, Major depressive disorder; HC, Healthy controls; HAMD, Hamilton depression rating scale; EQ-Vas, EuroQol Visual Analog Scale; PSS, Perceived Stress Scale; LTE-Q, List of Threatening Experiences Questionnaire; CTQ-SF, Childhood Trauma Questionnaire Short Form; BDI, Beck's Depression Inventory; BAI, Beck's Anxiety Inventory; GAD, General Anxiety Disorder scale; HAMA, Hamiton Anxiety Rating Scale; PANSS, Positive And Negative Syndrome Scale; GAF, Global Assessment of Functioning; PHQ, Patient Health Questionnaire; CES-D, Center for Epidemiologic Studies Depression Scale; HCL, Hypomania Checklist; MINI, Mini-International Neuropsychiatric Interview; PROMIS, Patient-Reported Outcomes Measurement Information System; C-SSRS, Columbia Suicide Severity Rating Scale; SITBI, Self-Injurious Thoughts and Behaviors Interview; QIDS, Quick Inventory of Depressive Symptomatology; QIDS-SR, Quick Inventory of Depressive Symptomatology Self-Reported; IDS, Inventory of Depressive Symptomatology; IDS-SR, Inventory of Depressive Symptomatology Self-Reported; MADRS, Montgomery Åsberg Depression Rating Scale; MDQ, Mood Disorder Questionnaire; RDP, Ribosomal Database Project; KEGG, Kyoto Encyclopedia of Genes and Genomes; NCBI, National Center for Biotechnology Information; HOMD, Human Oral Microbiome Database; BDNF, brain-derived neurotrophic factor; TRP, tryptophan; KYN, kynurenine; IDO, indoleamine 2,3-dioxygenase.

3.1. Characteristics of the selected studies

Among the selected studies, the groups were compared as follows: MDD vs HC 22 studies: (Fontana et al., 2020)(Bai et al., 2022)(H.-M. Chen et al., 2022)(M. mian Chen et al., 2023)(Chen et al., 2021)(Z. Chen et al., 2018)(Chung et al., 2019)(Dong et al., 2021)(Han et al., 2023)(Kovtun et al., 2022)(Lai et al., 2019)(Li et al., 2022)(Lin et al., 2023)(P. Liu et al., 2022)(R. T. Liu et al., 2020)(Maes et al., 2023b)(Rong et al., 2019)(Sun et al., 2022)(Tsai et al., 2022)(Ye et al., 2021)(Zhao et al, 2022.(P. Zheng et al., 2020)) (Yang et al., 2020)(Zheng et al., 2021); Acute MDD and Remission MDD vs HC (Caso et al., 2021); youngs MDD vs youngs HC, Middle aged MDD vs middle aged HC (Chen et al., 2020); Treatment resistant MDD, Treatment Responsive MDD, and untreated MDD vs HC (Fontana et al., 2020); Treatment Resistant MDD and Responder MDD vs HC (Gao et al., 2023a); Active-MDD and Responsed-MDD vs HC (Jiang et al., 2015); Major dysmood disorder and Simple dysmood disorder vs HC (Maes et al., 2023a). In total, 1352 patients diagnosed with MDD and 1284 individuals categorized as healthy controls are included in this review. The terminology used to describe the comparison groups is the same as that used by the authors in their respective studies, in order to preserve the intentionality of the comparisons and avoid possible confusion.

3.1.1. Quality of studies included

Most of the studies received a "Fair" quality rating (90%; N=26/29), while only two were rated as "Good" (7%; N=2/29) and one as "Poor" (3%; N=1/29), with the lack of adjustment for potential confounding variables being the most frequently found bias.

3.1.2. Country of study

Regarding the country of origin, there was a clear predominance of publications from China, accounting for 69% (20) of the studies included, followed by Taiwan with 10% (3) of the studies, and Thailand with approximately 7% (2). Spain, Italy, Russia, and the United States contributed 1 study, or approximately 3% each.

3.2. Microbiota analysis

Most of the studies used the Illumina MiSeq platform to sequence the samples (16 studies), but Illumina HiSeq2500 (4 studies), Illumina MiniSeq (2 studies), Illumina NovaSeq

6000 (2 studies), Roche 454 (2 studies), Illumina HiSeq X, (1 study), Illumina Novaseq PE250 (1 study), MinION Mk1C (2 studies), Illumina Novaseq unspecified (1 study) were also used.

For the taxonomic classification of microorganisms, 3 methodologies were identified: 22 studies sequenced the 16s rRNA region (76%), 6 opted for metagenomic sequencing of the samples (21%) and one study identified the microorganisms through a metaproteomic analysis (3.5%) (Chen et al., 2018). A total of 8 databases were used to identify the microorganisms, with RDP (Ribosomal Database Project) being the most prevalent, appearing in 12 studies, followed by Geengenes and Silva, both used in 6 studies each. The KEGG (Kyoto Encyclopedia of Genes and Genomes) database was used in 5 studies, NCBI RefSeq (National Center for Biotechnology Information reference Sequence Database) in 3 studies, HOMD (Human Oral Microbiome Database) and Ezbiocloud in 1 study each. One (1) study used a customized database , based on NCBI (Fontana et al., 2020)and one did not declare which database was used (Zheng et al., 2021).

3.3. Results of α and β diversity

Looking at the α-diversity results, the Shannon, Chao, Simpson, and ACE (Abundance-based Coverage Estimator) indices stand out as the most prevalent, present in 90%, 69%, 34% and 31% of the included studies, respectively. Among the studies, 45% highlighted at least one significantly different alpha-diversity index between the MDD and control groups, 45% did not present any significantly different index and 10% did not evaluate α-diversity. In contrast, when accounting for all 84 α-diversity indices evaluated, only 28% identified a significant difference between the groups. Of the 24 indices that showed a significant difference, 83% indicate a decreased α-diversity within the MDD group and 17% indicate a greater diversity in the depressive group.

In β-diversity assessments, the most frequent indices were Bray-Curtis dissimilarity, unweighted UniFrac distances, weighted UniFrac distances and jaccard dissimilarity, represented using PCoA (Principal Coordinates Analysis). Fifteen (52%) studies identified at least one significantly different index between the MDD and control groups, 11 (38%) found no significant differences between the groups and 3 (10%) did not carry out β-diversity assessments. Similarly, looking at all 40 indices present, 50% reported the presence of significant differences.

3.4. Relative abundance at phylum, family, and genus level

In the literature included, 80 genera, 56 families, 14 orders and 12 phyla were highlighted as differentially abundant, varying between more or less abundant in individuals with MDD. Among these, the genera *Faecalibacterium*, *Clostridium, Ruminococcus, Dialister, Anaerostipes* and *Roseburia*, the families *Oscillospiraceae, Prevotellaceae and Bacteroidaceae*, and the phylum *Bacillota* proved to be less abundant in MDD, with greater consistency than the other results. On the other hand, the genera *Bifidobacterium*, *Oscillibacter* and *Eggerthella*, the families *Bifidobacteriaceae* and *Enterobacteriaceae* and the phylum *Actinomycetota* were more abundant in MDD population, when compared to the control group. These results are detailed in Figures 2 and 3, which include taxa that appeared at least three times among studies and presented a 2 to 1 ratio of citations highlighting greater or lesser abundance. The complete set of abundance data can be found in supplementary data.

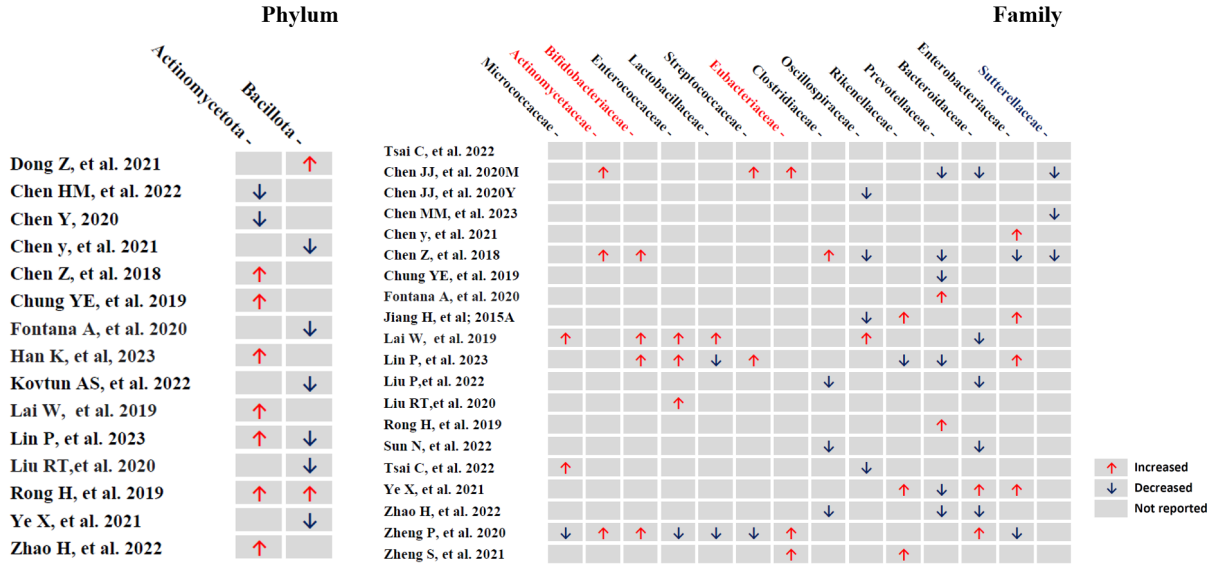

Fig. 2. Relative abundance at Phylum and Family level

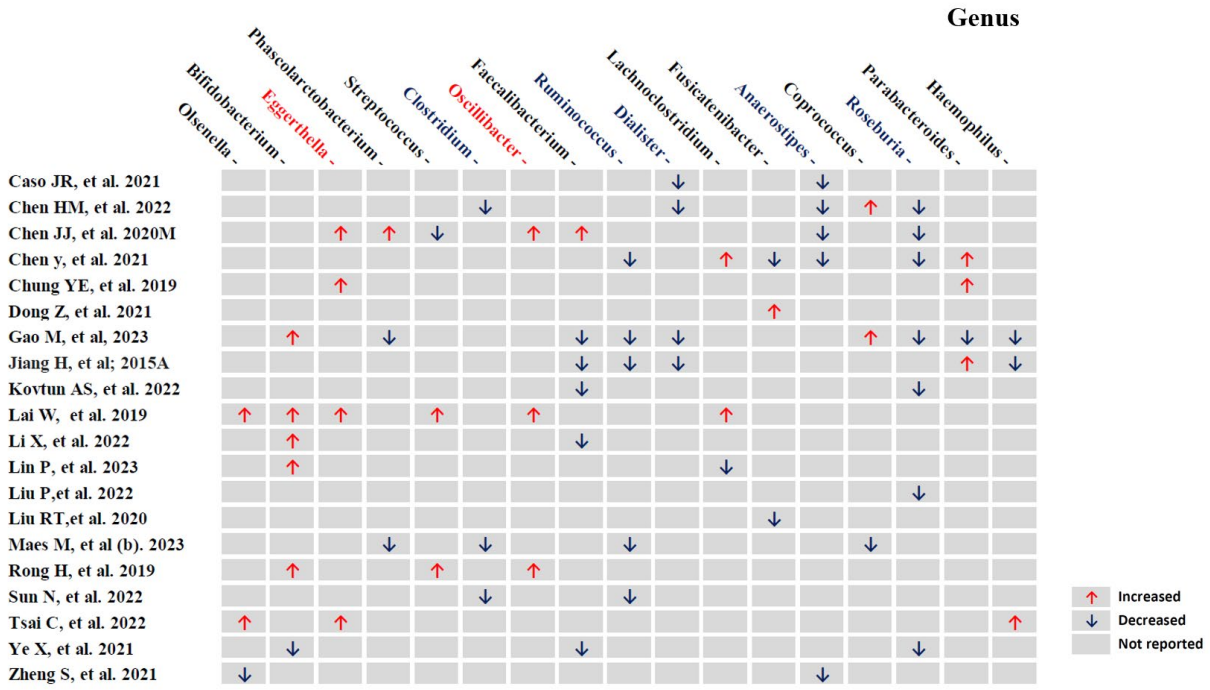

Fig. 3. Relative abundance at genus level

4. Discussion

4.1. α and β diversity

Alpha diversity summarizes the microbial community in individual samples, in terms of richness (number of species) and evenness (how well each species is represented) in the sample. Of the studies included, less than half identified at least one significantly different index between the MDD and control groups, and when evaluating the full set of α-diversity indices, only 28% found a significant difference. Thus, α-diversity, as reported by Gao et al. (2023b), McGuinness et al. (2022) and Sanada et al. (2020) does not appear to be a good differentiator between the MDD population and healthy individuals, indicating that a greater or lesser diversity of microorganisms, by itself, does not present a protective or harmful character (Shade, 2016).

In contrast, the assessment of beta diversity presents greater complexity precisely because it is a measure of inter-individual diversity that assesses the similarity of the communities compared to other samples, where not only the quantity but also the taxonomic groupings, influence the result. This analysis allows the grouping of microbial communities present in the samples to be visualized, revealing whether there is little or no overlap when compared to control samples, or whether they overlap, therefore suggesting that the two groups are not distinct (Pane et al., 2020).

Our results for β diversity show that 58% of the studies that evaluated beta diversity found significant differences between the MDD and control groups. Similarly, McGuinness et al. (2022) and Gao, Wang, et al. (2023) also report more consistent results of β-diversity differences in mental disorders and depression, while previous systematic reviews found differences with less consistency (Cheung et al., 2019)(Amirkhanzadeh Barandouzi et al., 2020)(Sanada et al., 2020)(Nikolova et al., 2021))(Vindegaard et al., 2021). Both α and β diversity, despite being used to indicate when there is a difference between groups, are not able to elucidate what these differences are at a taxonomic, physiological, metabolic, and clinical level, highlighting the need to explore in greater depth the differentially abundant taxa and their particularities.

4.2. Differentially abundant taxonomy and potential influence in major depressive disorder

Among the microorganisms identified as differentially abundant in individuals with MDD, the *Bacillota* (synonym *Firmicutes*) and *Bacteroidota* (synonym *Bacteroidetes*) phyla stand out, which together account for approximately 90% of the gut microbiota (Huang et al., 2018). Despite two studies showing the opposite, most of the literature identifies a lower abundance of the *Bacillota* phylum in the gut microbiota of humans with MDD, something that has been previously demonstrated in animal models, being reported less abundant in the gut microbiota of mouse models of depression (Yu et al., 2017) and significantly associated with stress-induced behavioral changes, also in mice (Bangsgaard Bendtsen et al., 2012). Regarding the *Prevotellaceae*, *Bacteroidaceae* and *Oscillospiraceae* families, most studies highlighted them as less abundant in the MDD group, and among them, Liang et al. (2022) cites *Oscillospiraceae* as more abundant in a bacterial group with low risk of developing MDD.

The most well-known pathophysiological mechanisms related to the influence of microbiota on MDD will be discussed below, as well as the main taxa related to each of these outcomes.

4.2.1. Inflammation

Multiple studies have investigated the correlation between pro-inflammatory markers and major depressive disorder, with an increase in the levels of Interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), Interleukin-1β (IL-1β) and C-reactive protein (CRP) being observed in depressed individuals (Milaneschi et al., 2020). It is also noteworthy that CRP,

when measured using a high sensitivity method, shows a moderate correlation with the development of MDD. Furthermore, Pasco et al. (2010) found that the hazard ratio (HR) for depression increased by 44% for each standard deviation increase in ln-hsPCR (log-transformed high-sensitivity C-reactive protein).

The increased production of pro-inflammatory cytokines is directly related to a decrease in tryptophan hydroxylase activity and an increase in indoleamine 2,3-dioxygenase (IDO) activity. As a result, the relationship between the strengthening of the inflammatory profile and the lower bioavailability of serotonin (5-HT) has gained the attention of the scientific world studying the factors involved in the pathophysiology of MDD (Savitz, 2017)(Brown et al., 2021).

Zeng et al. (2016) reports that a state of inflammation in the intestinal environment is particularly beneficial for the proliferation of *Enterobacteriaceae*, showing greater abundance in various inflammatory conditions such as irritable bowel syndrome, obesity, colorectal cancer, celiac disease, and antibiotic treatment. The *Enterobacteriaceae* family appears with increased abundance in individuals with MDD in four of the studies evaluated, in contrast to two others, which report the opposite. Painold et al. (2018), in a similar way to that described in our study, identified a higher abundance of these microorganisms during depressive episodes in patients with bipolar disorder.

The genus *Eggerthella*, more abundant in the population diagnosed with MDD in four studies, was correlated with depressive symptoms in a large-scale study, showing a causal relationship with MDD in a Mendelian randomization analysis. The genus can also synthesize serotonin and GABA (Radjabzadeh et al., 2022) and has been associated with inflammatory conditions (Forbes et al., 2018).

Recent studies indicate that the *Faecalibacterium* genus may represent 6.5% of the human microbiome, being prevalent in diverse human populations around the world and present in 85% of samples of intestinal origin (De Filippis et al., 2020). The decrease in its relative abundance is documented in multiple diseases, including colorectal cancer, dermatitis, gastrointestinal diseases and depression (Martín et al., 2023). Characterized as less abundant in the MDD group in five studies, the genus could potentially be protective against the disorder due to its anti-inflammatory properties (Sokol et al., 2008).

Similarly, bacteria belonging to the genus *Roseburia* were significantly reduced in the depressed population in seven of the studies evaluated, which raises a strong possibility that they contribute positively to the pathophysiology of MDD. The prevention of intestinal inflammation is highlighted as a possible protective mechanism, and has already been observed

in other pathologies, such as inflammatory bowel disease and type II diabetes mellitus (Nie et al., 2021). In rats, enteric administration of *Roseburia intestinalis* reduced depressive-like behavior, exerting a protective effect on the central nervous system and regulating inflammation via the gut-brain axis (Xu et al., 2021).

4.2.2. Kynurenine pathway

Dietary tryptophan (TRP) has two main destinations when interacting with the body. Less than 5% is directed towards the production of serotonin and more than 95% serves as a precursor for the kynurenine (KYN) pathway (Deng et al., 2021). Among the possible destinations of this pathway, kynurenic acid (KYNA), picolinic acid (PIC) and nicotinamide (NAM), are associated with neuroprotective effects are decreased in the serum of MDD patients, while quinolinic acid (QUIN) is associated with neurotoxicity when at high levels, in MDD. In addition, the proportion of neuroprotective metabolites in relation to neurotoxic ones is consistently decreased in the peripheral blood of individuals with major depressive disorder (Paul et al., 2022).

In the central nervous system this is especially relevant, especially when associated with a systemic inflammatory profile, since pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, interferon-alpha (IFN- α) and interferon-gamma (IFN-γ) increase the activity of the IDO enzyme, which degrades TRP, the main precursor of 5-HT, into QUIN, which acts as an NMDA agonist and stimulates the excessive release of GLU. Excessive exposure to cytokines, QUIN, reactive oxygen species (ROS) and reactive nitrogen species (RNS) leads to reduced expression of glutamate transporters, impaired glutamate reuptake and increased GLU release by astrocytes, as well as decreased production of neurotrophic factors such as BDNF. All these alterations result in an impairment of neural plasticity through excitotoxicity and apoptosis (Miller et al., 2009).

Fecal microbiota transplantation has been shown to influence the kynurenine pathway. Zhou et al. (2023) used the fecal microbiota of healthy adolescent volunteers for transplantation into mice that participated in a chronic stress protocol. The transplant significantly improved depressive-like behaviors, where *Roseburia* played an essential role, since its effective colonization of the colon resulted in an increase in 5-HT levels and a decrease in the toxic metabolites of kynurenine, quinolinic acid (Quin) and 3-hydroxykynurenine (3-HK), both in the brain and in the colon of the mice. In the same study, the abundance of the genus *Roseburia* was highly effective in predicting adolescent depression.

Thus, it is inferred that the intestinal microbiota can influence MDD positively and negatively, depending on its composition. For this, at least partially, inflammatory processes associated with the kynurenine pathway would be responsible.

4.2.3. Neurotransmitters and Short Chain Fatty Acids

Both the *Bifidobacteriaceae* family and the *Bifidobacterium* genus were characterized as more abundant in the intestinal microbiota of individuals in the MDD group in four and five publications, respectively, with only one study reporting a lower abundance of *Bifidobacterium*. The literature describes these microorganisms as a central genus involved in the production of GABA and glutamate (Altaib et al., 2021) and, contrastingly, has already been used as a probiotic in the treatment of depression (Johnson et al., 2023). Certain species of the genus even promote an increase in tryptophan levels in the body, such as *Bifidobacterium infantis* (Chen, et al., 2021)

On the other hand, a higher abundance of *Bifidobacterium* has already been reported in other mental disorders, such as bipolar disorder. A potential explanation for this phenomenon could be the ability of these microorganisms to produce lactic acid and lactate. When in high concentrations in the gut, these compounds have already been associated with acidosis, cardiac arrhythmia, and neurotoxicity. In addition, lactate, which can cross the blood-brain barrier, has been found in high concentrations in the brains of patients with MDD (McGuinness et al., 2022).

Moreover, bacteria such as *Clostridium* and *Roseburia* play an important role in directing tryptophan to the serotonin pathway, since the enterochromaffin-like cells (ECL), in which this conversion occurs, depend on the short-chain fatty acids (SCFA) (Góralczyk-Bińkowska et al., 2022) synthesized by these bacteria in the intestine. This raises the possibility that these microorganisms could influence MDD, by increasing neurotransmitter synthesis and through the kynurenine pathway, depending on the fate of tryptophan in the body.

Different bacteria have the ability to produce SCFAs, such as: *Clostridium spp., Eubacterium spp., Fusobacterium spp., Butyrivibrio spp., Megasphaera elsdenii, Mitsuokella multiacida, Roseburia intestinalis, Faecalibacterium prausnitzii,* and *Eubacterium halli* (Mirzaei et al., 2021). In addition to their role as an energy source for enterocytes and ECL, SCFAs also act to modulate lipid metabolism and glucose homeostasis, increase glucose

sensitivity, increase mitochondrial efficiency and function, contribute to body weight regulation, appetite reduction and inflammation regulation (Bourassa et al., 2016).

The term SCFA covers a group of carboxylic acids, with aliphatic tails comprising a variable number of carbon atoms between 1 and 6. Their production occurs mainly through the saccharolytic fermentation of carbohydrates that escape digestion and absorption in the small intestine, with the main products of this process being the SCFAs formate, acetate, propionate and butyrate (Morrison and Preston, 2016). Establishing the connection between microbial metabolic products and the CNS, SCFAs can cross the blood-brain barrier and participate in the metabolism of neurotransmitters. Frost et al. (2014) demonstrated that ^{13}C-labeled acetate from the intestinal fermentation of inulin can cross the blood-brain barrier, accumulate preferentially in the hypothalamus, and be incorporated into the neurotransmitters glutamate and GABA.

Both *Roseburia* (Nie et al., 2021)and *Faecalibacterium* have a significant capacity to produce AGCCs, with emphasis on the cross-feeding production of butyrate, mediated by acetate-producing bacteria (Rios-Covian et al., 2015)(D'hoe et al., 2018). Also the *Ruminococcus* genus has been described as part of a bacterial group at low risk of developing depressive symptoms (Liang et al., 2022) and capable of exerting a protective effect against MDD in a Mendelian randomization study. However, additional analyses did not corroborate this result (Chen et al., 2022). Their positive impact may be associated with maintaining a healthy intestinal environment through the degradation of polysaccharides into SCFAs (La Reau and Suen, 2018). Accordingly, it can be assumed that these taxa could contribute positively to major depressive disorder by producing SCFAs capable of influencing the metabolism of neurotransmitters such as GABA and Glutamate, and by directing tryptophan towards serotonin production.

The main differentially abundant taxa and their potential mechanisms of influence on major depressive disorder are shown in figure 4.

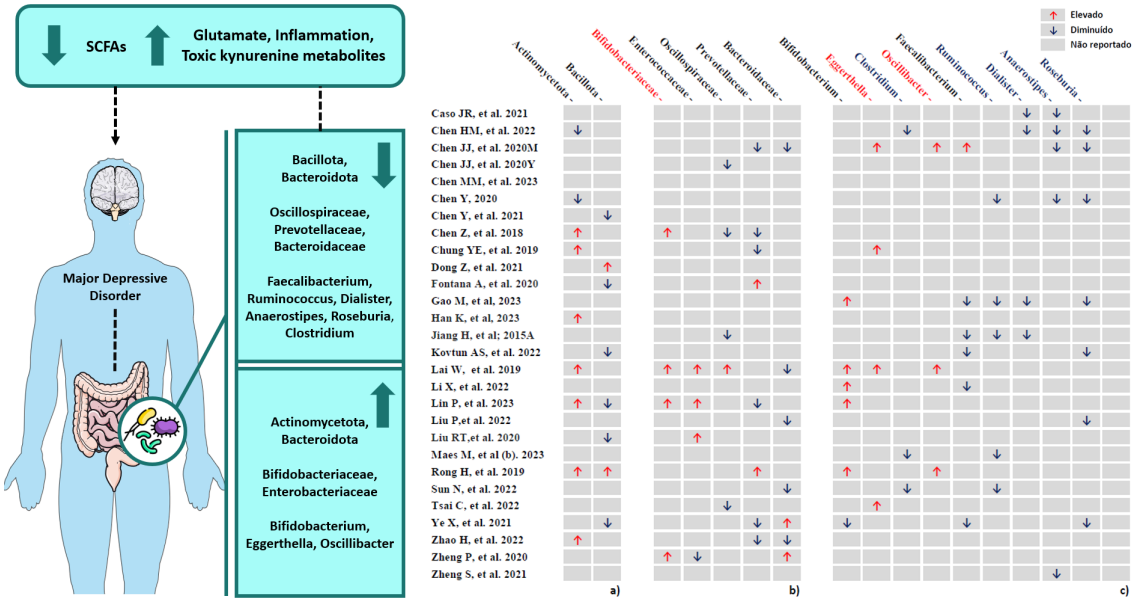

Fig. 4. Summary of the main differentially abundant taxonomies and their potential mechanisms of influence on major depressive disorder. A) Phylum level B) Family level C) Genus level. SCFAs: Short-chain fatty acids, GABA: Gamma-aminobutyric acid

This figure was partially constructed using Servier Medical Art (https://smart.servier.com), made available by Servier, licensed under Creative Commons Attribution 4.0 (https://creativecommons.org/licenses/by/4.0/). The image also used resources from Flaticon.com Bacteria icons created by Freepik - Flaticon.

4.3. Methodological heterogeneity and limitations

There is great methodological diversity among the included studies. Whether it is the platform used to sequence the samples, the processing of these genetic data, or the database used to compare the results and identify the microorganisms, these differences have an impact on the results of the studies (Siegwald et al., 2019)(Videnska et al., 2019). The sequencing platform is one of the sources of variation in results, with more recent platforms offering better coverage and lower costs, mainly replacing the Roche 454 platform (Degnan and Ochman, 2012). In our review, two studies used the Roche 454 platform (Chen et al., 2020)(Jiang et al., 2015).

Another example would be the use of 16S rRNA sequencing, which is most often used for taxonomic identification at the genus level, has low reliability for determining species and strains, and in these situations, is replaced by metagenomic sequencing strategies such as shotgun sequencing. Therefore, different studies may present conflicting results, partly due to

the methodology applied (Spichak et al., 2021), especially when considering that eight different databases were used among studies, including a customized database (Fontana et al., 2020).

Despite its higher resolution, shotgun metagenomic sequencing is more expensive (Jovel et al., 2016)(Greninger, 2018) and, as a result, the funding of the studies can directly impact the results presented, influencing the decision between the two strategies. As a reflection of this situation, it is noteworthy that only 6 of the 29 studies used the metagenomic sequencing methodology.

Finally, multiple external factors can influence the composition of the gut microbiota, mainly lifestyle and diet, followed by host genetics and geographical location (Parizadeh and Arrieta, 2023). For this reason, considering that China and Taiwan together account for 80% (N=23/29) of the studies included in this review, our results show a greater correlation with the intestinal microbiota from these populations.

5. Conclusion

Our findings suggest that alpha diversity indices cannot distinguish sufficiently well between populations with major depressive disorder and healthy individuals, and that greater or lesser non-specific diversity alone cannot characterize a harmful or protective gut microbiota. Despite presenting marginally better results, Beta diversity is still superficial in describing microbial diversity and its correlation to MDD, and more studies on its application are needed to better exploit its potential.

In the literature included in this review, multiple phyla, orders, families, and genera of microorganisms were described as differentially abundant in the gut microbiota, with emphasis on the genera *Faecalibacterium, Ruminococcus, Dialister, Anaerostipes, Clostridium* and *Roseburia,* the families *Oscillospiraceae, Prevotellaceae and Bacteroidaceae*, and the phylum *Bacillota*, which were less abundant in MDD in comparison with healthy controls. In contrast, the genera *Bifidobacterium, Oscillibacter and Eggerthella,* the families *Bifidobacteriaceae* and *Enterobacteriaceae* and the Phylum *Actinomycetota* were more abundant in the MDD population.

Regarding the influence of the intestinal microbiota on the pathophysiology of MDD, the main mechanisms involved seem to be associated with stimulating inflammation, activating the IDO enzyme and directing tryptophan metabolism toward the synthesis of neurotoxic kynurenine metabolites, quinolinic acid (Quin) and 3-hydroxykynurenine (3-HK). The positive

interaction between the intestinal microbiota and the gut-brain axis would be due to the anti-inflammatory potential of certain microorganisms; their influence on the metabolism of kynurenine by reducing its toxic metabolites; their ability to maintain intestinal integrity through the production of SCFAs as an energy source for colonocytes; and the production of SCFAs (such as acetate) capable of crossing the blood-brain barrier and participating in the production of neurotransmitters such as GABA and glutamate.

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5 CONCLUSÃO

Foi possível identificar que os índices de alfa diversidade não conseguem distinguir suficientemente bem entre populações com transtorno depressivo maior e indivíduos saudáveis, de forma que uma maior ou menor diversidade inespecífica não é, por si só, capaz de caracterizar uma microbiota intestinal prejudicial ou protetiva. A beta diversidade, apesar de apresentar resultados marginalmente melhores, ainda é superficial na descrição da diversidade microbiana, sendo necessários mais estudos acerca da sua aplicação para melhor explorar seu potencial.

Na literatura inclusa nesta revisão, múltiplos filos, ordens, famílias e gêneros de microrganismos foram descritos como diferencialmente abundantes na microbiota intestinal, com destaque para os gêneros *Faecalibacterium, Ruminococcus, Dialister, Anaerostipes, Clostridium* e *Roseburia,* as famílias *Oscillospiraceae, Prevotellaceae* e *Bacteroidaceae,* e o filo *Bacillota* que se mostraram menos abundantes no TDM em comparação com os controles saudáveis. Em contrapartida, os gêneros *Bifidobacterium, Oscillibacter* e *Eggerthella,* as famílias *Bifidobacteriaceae* e *Enterobacteriaceae* e o Filo *Actinomycetota* apresentaram maior abundância na população com TDM.

Com relação à influência da microbiota intestinal na fisiopatologia do TDM, os principais mecanismos envolvidos parecem estar associados ao estímulo de um quadro inflamatório, ativando a enzima IDO e direcionando o metabolismo do triptofano para a síntese de metabólicos neurotóxicos da quinurenina, o ácido quinolínico (Quin) e 3-hidroxiquinurenina (3-HK). Já a interação positiva entre a microbiota intestinal e o eixo intestino cérebro, se daria através do potencial anti-inflamatório dos produtos metabólicos de certos microrganismos; da sua influência no metabolismo da quinurenina ao reduzir seus metabólitos tóxicos; da sua capacidade de realizar a manutenção da integridade intestinal através da produção de AGCC como fonte de energia para os colonócitos; e da produção de AGCC (como o acetato) com capacidade de atravessar a barreira hematoencefálica e participar da produção de neurotransmissores como GABA e glutamato.

6 PERSPECTIVAS FUTURAS

- Elaborar um artigo de meta-análise dos dados de diversidade-alfa e beta dos artigos inclusos nesta revisão.

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8. ANEXO

Psychiatry Research

Alterations in Gut Microbiota in Major Depressive Disorder: A Systematic Review

--Manuscript Draft--

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Keywords:	Major depressive disorder; Gut microbiota; Relative abundance; Inflammation; Kynurenine; SCFA; Neurotoxicity
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Abstract:	A growing body of data establishes a connection between the gut microbiota and the development and functioning of the central nervous system, pointing to a bidirectional communication system associated not only with intestinal homeostasis but also with certain mental disorders, such as major depressive disorder (MDD). In this systematic review, we consolidate information from the current literature regarding the composition of the gut microbiota in individuals with major depressive disorder compared to healthy controls, focusing on measures of alpha and beta diversity, as well as the phyla, orders, families, and genera that are differentially abundant between these groups. Twenty-nine studies were identified, encompassing 1,352 patients with MDD and 1,284 control individuals. Our investigation suggests no consistent differences in alpha diversity (both in terms of richness and evenness) between the MDD and healthy populations. In contrast, beta diversity results appear to distinguish between these groups more reliably. Additionally, we found that certain microbial taxa were consistently less abundant in the MDD population. These taxa included groups that could synthesize short-chain fatty acids (SCFAs), taxa with anti-inflammatory potential, and taxa associated with reducing toxic kynurenine metabolites. Conversely, taxa associated with pro-inflammatory characteristics, IDO enzyme activation, and directing tryptophan metabolism towards the synthesis of neurotoxic kynurenine metabolites, were more abundant in the MDD group than in healthy controls.

Anexo. Comprovante de submissão do artigo.