UNIVERSIDADE DE BRASÍLIA
FACULDADE DE CEILÂNDIA
CURSO DE FARMÁCIA

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PAPEL DOS LIPÍDIOS DA MICROBIOTA INTESTINAL NO DESFECHO FENOTÍPICO E PERSPECTIVAS TERAPÊUTICAS

ROLE OF INTESTINAL MICROBIOTA LIPIDS IN PHENOTYPIC OUTCOME AND THERAPEUTIC PERSPECTIVES

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Monografia de Conclusão de Curso apresentada como requisito parcial para obtenção do grau de Farmacêutico, Faculdade de Ceilândia,. Universidade de Brasília,

Orientador: Prof. Dr. Guilherme Martins Santos

BRASÍLIA, 2021

Ficha catalográfica elaborada automaticamente,
com os dados fornecidos pelo(a) autor(a)

Valim Carneiro, Pâmela
Vr ROLE OF INTESTINAL MICROBIOTA LIPIDS IN PHENOTYPIC OUTCOME AND THERAPEUTIC PERSPECTIVES / Pâmela Valim Carneiro; orientador Guilherme Martins Santos. -- Brasília, 2021.
66 p.

Monografia (Graduação - Farmácia) -- Universidade de Brasília, 2021.

1. Microbiota. 2. Lipídios. 3. Dieta. 4. Fezes. 5. Metabólitos. I. Martins Santos, Guilherme, orient. II. Título.

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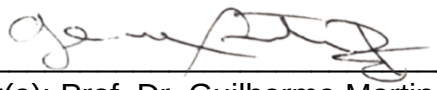

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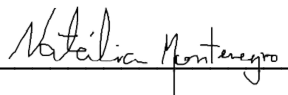

Ma. Natália de Aguiar Montenegro
Universidade de Brasília

BRASÍLIA, 2021

Dedico este trabalho à minha família, por todo amor, suporte, estímulo e compreensão.

AGRADECIMENTOS

Em primeiro lugar agradeço a Deus, que me sustentou durante esse ciclo, com fôlego de vida, com sua paz mesmo em meio à tempestade e seu amor incondicional.

Agradeço à minha família, que me encorajou em todo o momento, me trazendo ânimo e acreditando em mim quando eu mesma não enxergava meu valor.

Agradeço ao meu noivo, Amós, que esteve ao meu lado durante todos os altos e baixos. Que acolheu meu choro, comemorou minhas alegrias e me incentivou a dar o melhor de mim.

Agradeço ao meu orientador, Dr. Guilherme Martins Santos, por me acolher em seu grupo de pesquisa e constantemente me inspirar com sua paixão à pesquisa, à ciência e aos detalhes fascinantes.

Agradeço à mentoria essencial da Ma. Natália de Aguiar Montenegro, por todos os ensinamentos, palavras de encorajamento, além da colaboração intelectual.

E por fim, aos meus colegas da XVII turma de farmácia da FCE, pois sem o suporte deles, não teria chegado até aqui.

“Quanto mais eu estudo a natureza, mais eu
fico maravilhado com as obras do Criador.
A ciência me aproxima de Deus.”
(Louis Pasteur)

RESUMO

O transplante fecal tem se mostrado eficaz para o tratamento de várias patologias, como síndrome metabólica e distúrbios neurológicos. No entanto, a transferência de organismos vivos patogênicos, principalmente bactérias, limita seu uso terapêutico. Assim, o estudo de metabólitos da microbiota intestinal pode oferecer uma nova estratégia terapêutica para auxiliar no tratamento de diversas doenças. Além disso, os lipídios parecem ter o maior impacto na regulação de várias vias de sinalização celular, incluindo vias da inflamação. Portanto, o estudo de metabólitos lipídicos da comunidade microbiológica intestinal e seus constituintes são áreas promissoras para investigação detalhada.

Palavras-chave: Microbiota; Lipídios; Dieta; Fezes; Metabólitos; Terapêutica.

ABSTRACT

Fecal transplantation has been shown to be effective for the treatment of various pathologies, such as metabolic syndrome and neurological disorders. However, the transfer of pathogenic living organisms, mainly bacteria, limits their therapeutic use. Thus, the study of metabolites of the intestinal microbiota may offer a new therapeutic strategy to assist in the treatment of various diseases. Furthermore, lipids seem to have the greatest impact on the regulation of several cell signaling pathways, including pathways of inflammation. Therefore, study of lipid metabolites of the intestinal microbiological community and its constituents are promising areas for detailed investigation.

Keywords: Microbiota; Lipids; Diet; Feces; Metabolites; Therapeutic.

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS E SIGLAS

BA	Bile acid
FDA	Food and Drug Administration
GPCR	G-protein coupled receptors
HAT	Histone acetyltransferases
HCA_2	Hydroxycarboxylic acid receptor 2
HDAC	Histone deacetylases
IBD	Inflammatory bowel disease
LCA	Lithocholic acid
LPS	Lypopolyssaccharide
PC	Phosphatidylcholine
PA	Phosphatic acid
PE	Phosphatidylethanolamine
PG	Phosphatidylglycerol
PI	Phosphatidylinositol
PS	Phosphatidylserine
NKT	Natural Killer
SCFA	Short-chain fatty acid
TNF-α	Tumor Necrosis Factor -Alpha
TLR_4	Toll-like receptor 4
TMAO	Trymethylamine-N-oxide

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1 INTRODUÇÃO

Na década de 70, estimou-se que 90% as células presentes em um corpo humano eram inerentes à população de organismos microscópicos que habitam nele (SAVAGE, 1977). Fontes atuais estimam que a proporção do número de células humanas e células bacterianas seja próximo de 1:1 (SENDER, 2016). Seja qual for a proporção real, a influência de microrganismos no corpo humano é notória e relevante para a saúde de seu hospedeiro. Bactérias, fungos, vírus e arqueas estão distribuídos em diversos órgãos e superfícies, como pele, trato respiratório, reprodutivo e gastrintestinal, numa relação de simbiose, em que ambas as partes se modulam mutualmente (O'HARA; SHANAHAN, 2006). À essa comunidade de microrganismos presentes em um organismo, dá-se o nome de microbiota. A microbiota é considerada por alguns autores como um órgão do corpo humano, uma vez que é composto por diferentes linhagens celulares que se comunicam entre si; consomem, armazenam e redistribuem energia; e possuem funções metabólicas (BÄCKHED et al., 2005). Sendo assim, a microbiota é indispensável para a manutenção fisiológica do organismo.

O trato gastrintestinal apresenta uma rica microbiota, com uma grande variação de quantidade e tipos de espécies, principalmente de bactérias. Estima-se que entre 15-35 mil espécies de bactérias colonizam o intestino de um indivíduo adulto (FRANK et al., 2007), sendo a maioria pertencentes aos filos Firmicutes e Bacteroidetes (LEY et al., 2005). As bactérias da microbiota são responsáveis por diversas funções metabólicas, como captação de energia através da degradação de carboidratos, fermentação de polissacarídeos, regulação do metabolismo dos ácidos biliares e da colina, além de regulação da permeabilidade intestinal e inflamação de tecidos periféricos (TREMAROLI; BÄCKHED, 2012).

Alterações na microbiota, ou disbioses, resultam do desbalanço entre as proporções de bactérias dos filos mais comuns no intestino (WEISS; HENNET, 2017). As disbioses têm sido associadas a alterações fenotípicas, como doenças infecciosas, inflamatórias e metabólicas, como por exemplo a obesidade (CANI et al., 2009; MAZMANIAN et al., 2005; SERINO et al., 2012).

Apesar da grande relevância fisiológica e terapêutica, os mecanismos moleculares dessa interação com o hospedeiro ainda estão sendo desvendados. Na última década, pesquisas têm buscado identificar os metabólitos que têm direta influência sobre a homeostase e estado de saúde do indivíduo (DONIA; FISCHBACH, 2015). Exemplos de metabólitos são aminoácidos, ácidos biliares, polissacarídeos, vitaminas e lipídios, como ácidos graxos de cadeia curta e longa (SUEZ; ELINAV, 2017). As moléculas lipídicas estão entre os metabólitos da microbiota intestinal que participam da regulação de diversas vias de sinalização do metabolismo celular, atuando como substratos para receptores de membrana e nuclear (FERNANDES et al., 2018; NGUYEN et al., 2017). A produção, mecanismos e atuação de alguns metabólitos lipídicos da microbiota intestinal, como os ácidos graxos de cadeia curta (SCFA), já foram elucidados (MARTIN-GALLAUSIAUX et al., 2021), entretanto, sua relevância na terapêutica ainda não foi caracterizada completamente.

A aplicação de terapias que envolvam os metabólitos de microbiota pode ser vantajosa pela possibilidade de eliminar a patogenicidade associada a utilização de microrganismos vivos indesejados (LEE; HASE, 2014), como já relatado em transplante de microbiota fecal (FOOD AND DRUG ADMINISTRATION, 2020), em que podem ser transferidos tanto microrganismos benéficos, como patogênicos. Desta forma, o estudo de metabólitos lipídicos da microbiota intestinal mostra-se promissor para a identificação de novas moléculas com funções terapêuticas e intervenções personalizadas (KASHYAP et al., 2017).

Ao nascer, o trato intestinal do nascituro é estéril e começa a ser colonizado nos primeiros dias de vida (PALMER et al., 2007). A microbiota é um órgão que apresenta grande plasticidade e adaptabilidade, com composição única a cada indivíduo (ZHU et al., 2015). A composição da microbiota varia de acordo com o grupo populacional em que o indivíduo está inserido, predisposições genéticas, dieta. A composição da microbiota é dependente de fatores ambientas como dieta do hospedeiro, idade e uso de antibióticos (JANDHYALA et al., 2015), e a sua população varia entre as porções do intestino, sendo o cólon a região com maior quantidade populacional de bactérias (revisado em DETHLEFSEN; MCFALL-NGAI; RELMAN, 2007). Uma microbiota saudável tem sido associada a abundância de bactérias

pertencentes aos gêneros Bacteroides, Prevotella e Ruminococcus (HOLLISTER; GAO; VERSALOVIC, 2014).

De maneira geral, a microbiota intestinal exerce funções relacionadas à regulação do armazenamento de energia, proteção contra danos ao epitélio intestinal e estimulação da angiogênese (ECKBURG et al., 2005). Os organismos comensais influenciam na absorção de nutrientes, promovem proteção contra agentes patogênicos, metabolizam drogas e xenobióticos, contribuem com modelação do sistema imunológico e propiciam a integridade do ambiente intestinal e sua estrutura (JANDHYALA et al., 2015). O metabolismo da comunidade microbiológica é intimamente ligado com a do seu hospedeiro, garantindo sobrevivência dos microrganismos enquanto contribui com diversas vias metabólicas do ser humano.

Bactérias intestinais se beneficiam do comensalismo nas diferentes regiões do trato gastrointestinal. As bactérias têm como fonte de energia carboidratos, glicoproteínas e outras macromoléculas derivadas da dieta. Polissacarídeos complexos provenientes de células vegetais e amidos resistentes, por exemplo, não digeríveis pelo arcabouço enzimático do hospedeiro são catabolizadas por enzimas de microrganismos, transformando-as em partículas absorvíveis como vitaminas e ácidos graxos de cadeia curta, que contribuem para a nutrição do organismo humano (TREMAROLI; BÄCKHED, 2012). O padrão da fermentação e consequentemente dos metabólitos a serem excretados, dependem da composição e diversidade de microrganismos da microbiota.

Entretanto, por sofrer alterações ambientais, a microbiota pode apresentar desequilíbrios. As bactérias dos filos Firmicutes e Bacteroidetes são predominantes e a proporção entre as bactérias envolvidas vêm sendo associadas a predisposição à diversas doenças, principalmente obesidade (LEY et al., 2006). O exemplo dos filos Firmicutes e Bacteroidetes demostra que o desbalanço entre grupos hegemônicos pode levar a quadros patológicos.

As disbioses, provenientes da diminuição de microrganismos ou da perda variedade de espécies, têm sido associadas a diversas doenças. A disbiose pode se estabelecer através de fatores como modulação da dieta, infecção intestinal, genética do hospedeiro, além de fatores ambientais (LEVY 2015). Um recente estudo

identificou através de metagenômica quantitativa as características que diferenciam a microbiota de acordo com sua variabilidade genética e suas implicações na saúde e doença (LE CHATELIER et al., 2013).

No estudo de Le Chatelier, a análise metagenômica de microbiota de indivíduos não obesos e obesos evidencia que a microbiota geneticamente empobrecida é inclinada a desenvolver quadros inflamatórios devido a fatores como: redução de bactérias produtoras de butirato, aumento na degradação de muco, redução no potencial de produção de hidrogênio e metanol, aumento de espécies patogênicas (como *Campylobacter spp*. e *Shigella spp*.), e aumento de peroxidases (LE CHATELIER et al., 2013). Entre as doenças mais associadas a quadros inflamatórios crônicos estão as síndromes intestinais inflamatórias, como doença de Crohn e colite ulcerativa, obesidade e até asma (FERREIRA et al., 2014).

Com a modificação da diversidade da microbiota há também modificações entre os metabólitos produzidos por ela. Dessa forma, há uma alteração também em perfis metabólicos presentes no hospedeiro. Em recente estudo, mostrou-se através de sequenciamento do gene 16S rRNA de amostras fecais e de língua que há alterações entre a microbiota bucal e perfil lipídico de pacientes com COVID-19 e indivíduos saudáveis, assim como alterações na microbiota intestinal (REN et al., 2021).

Entre as moléculas produzidas pela microbiota existe a classe lipídica. Os lipídios são responsáveis por processos metabólicos importantes para a homeostase do hospedeiro, como discutido posteriormente. Estudos mais aprofundados de como ocorre esse balanço entre microbiota-lipídios-hospedeiro poderiam trazer novas propostas terapêuticas não invasivas e de fácil acesso.

2 REVISÃO DE LITERATURA

Lipídios são moléculas biológicas hidrofóbicas ou, em alguns casos, anfifílicas que podem exercer funções variadas, como armazenamento de energia, composição estrutural e sinalização bioquímica inter e intracelular (VANCE; VANCE, 2008), sendo

fundamentais para a manutenção da fisiologia humana. A literatura evidencia que moléculas lipídicas estão intimamente envolvidas com processos inflamatórios e na regulação do curso destes e, portanto, estão sendo associados à patofisiologia de diversas doenças de cunho inflamatório (CHIURCHIÙ; LEUTI; MACCARRONE, 2018).

O recente interesse da comunidade científica pela microbiota tem suscitado perguntas sobre a possível atuação e influência de metabólitos da microbiota na saúde do indivíduo. A revisão de J. Nicholson e colaboradores (2012) discute o assunto e suscita a importância dos metabólitos de microbiota, inclusive lipídicos, correlacionando-os com suas funções metabólicas no hospedeiro .

A análise da lipidômica tem sido utilizada para a ampliação do conhecimento sobre as funções específicas de lipídios em sistemas biológicos e suas contribuições em cascatas de sinalização, e no contexto patológico, sendo um instrumento inovador importante para a previsão de intervenções terapêuticas (NGUYEN et al., 2017; YASUDA et al., 2020).

A melhor caracterização dos metabólitos lipídicos de microbiota é uma área de estudo promissora, uma vez que participam de diversas vias metabólicas, sendo indispensáveis para homeostase do hospedeiro, e alterações relacionadas a moléculas lipídicas se entrelaçam com a etiologia de diversas doenças.

2.1 Ácidos Graxos de Cadeia Curta (SCFA)

Os ácidos graxos de cadeia curta, ou SCFA, são os metabólitos de microbiota mais elucidados. Os SCFA, ácidos graxos de até 6 carbonos, são produzidos através de fibras de carboidratos complexos ou proteínas e peptídeos não digeríveis presentes na dieta do hospedeiro que chegam até o cólon sem serem absorvidas ou digeridas no trajeto (CUMMINGS, 1973). Bactérias localizadas majoritariamente no cólon promovem a fermentação desses substratos formando SCFA, como acetato, propionato, butirato, dentre outros. O tipo e quantidade de SCFA produzido depende de fatores como o tempo de trânsito do quilo no intestino, a quantidade e o tipo de

bactérias da microbiota do organismo, além da composição dietética do hospedeiro (SITTIPO; SHIM; LEE, 2019).

No organismo do hospedeiro, os SCFA podem ter diferentes funções dependendo a sua concentração e local da absorção. Quando absorvidos, podem ser utilizados como fonte de energia e como substratos para lipogênese, gliconeogênese e síntese de colesterol, atuar como moduladores de inflamação, atuam como vasodilatadores melhorando a motilidade intestinal e contribuem para a integridade da mucosa, dentre outras aplicações que estão sendo elucidadas (SARTOR, 2008). A maioria das funções citadas tem como mecanismo principal a regulação gênica provocada pelo SCFA. O butirato e o propionato apresentam capacidade de inibir as enzimas lisina e histona desacetilase (HDAC) enquanto metabólitos do butirato aumentam a atividade de acetiltransferases (HAT) (DONOHOE et al., 2012). Ambos os mecanismos propiciam a acetilação de histonas, promovendo a abertura da cromatina propiciando a transcrição gênica. Foi demonstrado que o butirato também possui capacidade de inibir a fosforilação e metilação de histonas, influenciando na progressão do ciclo celular (BOFFA; GRUSS; ALLFREY, 1981).

Diversos estudos têm demonstrado desfechos favoráveis a suplementação dietética de fibras resistentes que favorecem a produção de SCFA, provocando alteração em fenótipos relacionados a obesidade (MAYENGBAM et al., 2019), câncer colorretal (BISHEHSARI et al., 2018), diabetes (XU et al., 2018), dentre outros.

2.2 Lipopolissacarídeos (LPS)

O lipopolissacarídeo (LPS) é o principal componente da membrana externa de bactérias Gram-negativas (MAYEUX, 1997). O LPS age no hospedeiro como um potente estimulante da imunidade inata, inflamação e proliferação epitelial pela ativação de toll-like receptors (TLRs). Os TLRs induzem a formação de cicloxigenases e prostaglandinas, que atuam em resposta a danos à mucosa ativando a proliferação celular do epitélio e apoptose (FUKATA et al., 2006). Mostrou-se também que o LPS estimula células globulares do epitélio intestinal a produzir mucinas, proteínas que

formam o muco que protege a mucosa intestinal de danos físicos, químicos, e enzimáticos (ENSS et al., 1996; SMIRNOVA et al., 2003).

Sabe-se que o estreitamento da camada de muco no intestino confere maior susceptibilidade a doenças inflamatórias intestinais, como Doença de Crohn e colite ulcerativa (PETERSSON et al., 2011). Foi constatado em modelo animal com ausência de microbiota que a administração de LPS ou PGN (peptidoglicanos) restaurou a camada de muco à níveis normais, apenas 40 minutos de exposição (J. PETERSSON et al., 2011). A camada de muco reduzida facilita a aderência dos microrganismos presentes ao epitélio intestinal, ativando cascatas de sinalização da inflamação (HEAZLEWOOD et al., 2008). Todavia, ainda não se sabe se um fator determinante para o desenvolvimento da colite ulcerativa é a destruição da camada de muco e, consequentemente, o contato de bactérias intestinais com a mucosa ou se a inflamação das mucosas devido ao contato com as bactérias do lúmen leva ao estreitamento da barreira de muco (KOBAYASHI et al., 2020).

Apesar dos fatores benéficos provocados pela presença de LPS, os mesmos podem trazer malefícios ao organismo em quadros de disbioses. Quando as concentrações de LPS se elevam ou há aumento na quantidade de receptores TLR, ocorre a superestimulação dos receptores TLR, que levam a um estado inflamatório contínuo (CANI et al., 2007). Sabe-se que o estado inflamatório crônico eleva o risco de desenvolvimento de doenças como obesidade, síndrome do intestino irritável e câncer colorretal (CALLE; KAAKS, 2004). Disbiose envolvendo o aumento de bactérias produtoras de LPS foram recentemente associadas à resposta inflamatória aumentada em pacientes acometidos de COVID-19 (REN et al., 2021).

2.3 Ácidos Biliares

Os ácidos biliares são lipídios produzidos no fígado derivados do colesterol. Os ácidos biliares são excretados pela bile no duodeno e facilitam a digestão, uma vez que possuem uma ação detergente, emulsionando a gordura presente na dieta (DI CIAULA et al., 2017), entretanto, sua função no organismo não é restrita a essa. Os ácidos biliares primários (ácido cólico e ácido quenodesoxicólico) são conjugados

com taurina ou glicina antes de serem armazenados na glândula biliar (FALANY et al., 1994). No intestino delgado mais de 90% dos ácidos biliares são reabsorvidos e retornam ao fígado pela circulação entero-hepática, entretanto, em torno de 5% a 10% deles continuam até o cólon, onde são modificados pela microbiota local (GÉRARD, 2013). Bactérias dos gêneros Bacteroides, Eubacterium, e Clostridium possuem enzimas que promovem a desconjugação da taurina e da glicina e hidrólise possibilitando a formação de ácidos biliares secundários (ácido desoxicólico e ácido litocólico) mais lipofílicos que são reabsorvidos pelo epitélio intestinal e entram na circulação (GÉRARD, 2013)

Os metabólitos da interação microbiota hospedeiro (ácidos biliares primários e secundários) ligam-se a receptores nucleares hormonais presentes em várias linhagens celulares, como enterócitos, hepatócitos e adipócitos chamados de receptores Farnesoide X (FXR) (SCHAAP; TRAUNER; JANSEN, 2014). A ativação de receptores Farnesoide X implica na regulação de genes associados à síntese e transporte de ácidos biliares, ao metabolismo de carboidratos e a regulação da imunidade inata intestinal (JOYCE; GAHAN, 2016). Por meio da ativação do receptor FXR, metabólitos de microbiota podem atuar reduzindo lipogênese, aumentando a oxidação de ácidos graxos e promovendo a remoção de triglicerídeos no plasma, reduzindo assim o risco de desenvolvimento de doenças metabólicas (LI; CHIANG, 2014).

O metabolismo dos ácidos biliares possui um importante papel fisiológico, podendo impactar o organismo de forma benéfica ou contribuindo para quadros patológicos dependendo da quantidade e tipo de ácidos biliares secundários produzidos. Alterações envolvendo o metabolismo de ácidos biliares foram associados com doenças inflamatórias intestinais, como doença de Crohn e colite ulcerativa, e metabólicas, como diabetes e obesidade (LABBÉ et al., 2014) além de câncer colorretal (KANDELL; BERNSTEIN, 1991). A disbiose observada na colite ulcerativa leva à redução da desconjugação e dessulfatação de ácidos biliares, levando a uma composição e concentração alterada destes podendo contribuir para o quadro inflamatório (DUBOC et al., 2013).

Por outro lado, o potencial de promover dano a membranas e ao DNA, e estresse oxidativo causado pelos ácidos biliares confere a eles propriedades antibacterianas contra patógenos como *Clostridium difficile* (BEGLEY; GAHAN; HILL, 2005), sendo portanto, importantes reguladores da população da microbiota.

2.4 Fosfolipídios

Os fosfolipídios são componentes de membranas celulares que, além de possuírem função estrutural, estão envolvidos em diversos tipos de sinalização celular, incluindo expressão gênica (FERNANDES et al., 2018). A fosfatidilcolina é um tipo de fosfolipídio importante na composição de membrana de células mamíferas e de lipoproteínas (GIBELLINI; SMITH, 2010). Quando presente na dieta, a fosfatidilcolina é metabolizada no intestino pela microbiota presente para produção de trimetilamina (TMA), que posteriormente é oxidada por enzimas hepáticas formando n-óxido de trimetilamina (TMAO) (YU et al., 2019).

O aumento de TMAO tem sido associado a riscos cardiovasculares (TANG et al., 2013). Entretanto, um recente trabalho por Haining Yu e colegas (2019) revela que a suplementação de fosfatidilcolina na dieta de ratos saudáveis resultou em remodelamento da microbiota sem que houvesse alteração na síntese de TMAO e seus níveis plasmáticos. Os resultados desse trabalho também indicam que a suplementação melhora os níveis de inflamação por meio da regulação de LPS e SCFA (YU et al., 2019).

2.5 Esfingolipídios

Esfingolipídios são importantes componentes de membrana plasmática de eucariotos e alguns procariotos que modulam interações célula-célula e atuam no reconhecimento celular (HANNUN; OBEID, 2008). Os esfingolipídios mais elucidados são as ceramidas, precursoras dos outros tipos, esfingosina e a esfingosina-1-fosfato (S1P). Moléculas de esfingolipídios são produtos da união dos aminoácidos serina,

alanina ou glicina, com o palmitoil-CoA, podendo ser transformados de ceramidas em moléculas mais complexas, como esfingomielina, glicoesfingolipídios, ceramida-1-fosfato (C1P) ou S1P (LEHNINGER, 2014)

Os esfingolipídios desempenham as mais diversas funções celulares, incluindo crescimento, ciclo, senescência e morte celular; resposta inflamatória, adesão e migração celular, aquisição de nutrientes, resposta ao estresse, autofagia e metabolismo celular. Dentre as atribuições citadas, a referente à sua influência no sistema imunológico e suas funções relacionadas à inflamação, é a mais bem estabelecida (SPIEGEL; MILSTIEN, 2011).

Certos grupos de bactérias anaeróbicas possuem esfingolipídios como componentes estruturais de suas membranas, principalmente as pertencentes as do gênero Bacteroides (OLSEN; JANTZEN, 2001). Os metabólitos de Bacteroidetes associados à classe dos esfingolipídios participam da modulação de células T *Natural Killer* (NKT) (AN et al., 2014), recrutadas em processos inflamatórios. Um estudo de Eric M. Brown (2019) verificou correlação entre deficiência de esfingolipídios bacterianos e doenças inflamatórias intestinais, corroborando com o protagonismo de metabólitos lipídicos no estado de saúde do seu hospedeiro

A modulação da composição lipídica de membranas celulares tem sido estudada como possível alvo terapêutico para tratamento de diversas doenças, como obesidade, diabetes, hipercolesterolemia e outras síndromes metabólicas; e até doenças cardiovasculares e neurodegenerativas, como indica a revisão de Pablo V. Escribá e colaboradores (2015).

Por outro lado, a suplementação dietética de esfingolipídios presentes no leite e ovos tem se mostrado promissora para o manejo de doenças crônicas relacionadas à inflamação. Foi demonstrado sua influência na inibição da absorção intestinal de lipídios (NOH; KOO, 2004), ativação de receptores nucleares associados a inflamação (MAZZEI et al., 2011) e modulação da microbiota (NORRIS et al., 2016).

2.6 Tratamento

A proposição da influência positiva dos microrganismos na saúde de um indivíduo foi feita por Elie Metchnikof, que descreve pela primeira vez os efeitos benéficos que bactérias da família Lactobacillus poderiam proporcionar (revisado em METCHNIKOFF; MITCHELL, 1908). A proposta revolucionária deu origem aos probióticos e prebióticos, que são microrganismos vivos e componentes alimentares não digeríveis, respectivamente, que atuam reestabelecendo o equilíbrio da microbiota aumentando a população de microrganismos benéficos (STEER et al., 2000). Apesar de promissores, entretanto, ensaios clínicos randomizados mais robustos ainda são necessários para afirmar os mecanismos de ação e a eficácia desses tratamentos por serem muito dependentes da cepa utilizada, no caso dos probióticos, e das características inerentes aos hospedeiros tratados, no caso dos prebióticos (SANDERS et al., 2019)

O fenótipo associado a doenças mostrou-se transmissível através de transferência de microbiota. Nesse contexto, surge a terapia baseada no transplante fecal de microbiota (TFM), que tem sido utilizado para o tratamento de distúrbios associados à microbiota, como infecção por *Clostridium difficile*, doença inflamatória intestinal e síndrome de Crohn (BONOMO et al., 2020; MAZZAWI et al., 2019). O transplante de microbiota consiste na transferência de microrganismos de um doador saudável, que pode ser realizada via endoscopia ou por via oral através de cápsulas. Os pacientes submetidos ao transplante devem ser monitorados após a terapia devido a possibilidade de manifestação de efeitos adversos como infecções por patógenos que podem levar até a morte, e estão presentes de 28,5% dos casos (WANG et al., 2016). Embora a terapia venha sendo utilizada de maneira eficaz para o tratamento de infecção recorrente por *C. difficile*, ensaios clínicos adicionais são necessários para analisar a utilidade do transplante fecal de microbiota para o tratamento de outras doenças, como obesidade e diabetes (SMITS et al., 2013).

Entretanto, a evolução da medicina tem se direcionado para tratamentos cada vez mais individualizados e específicos para as necessidades do indivíduo. A engenharia da microbiota é um desafio para o futuro e moléculas lipídicas possuem grandes vantagens como fármacos reguladores de microbiota.

Apesar do grande potencial terapêutico da microbiota intestinal, conforme mencionado, o transplante fecal pode também conter organismos vivos patogênicos que podem ser até mesmo letais ao receptor. Recentemente, a FDA (Food and Drug Adminstration), agência federal americana do Departamento de e Serviços Humanos Saúde, suspendeu diversos procedimentos que utilizavam a terapia de transplante fecal devido ao óbito de um paciente, e outro que adoeceu gravemente (FOOD AND DRUG ADMINISTRATION, 2020). Análises das amostras das fezes do doador mostraram a presença de *Escherichia coli* resistentes a antibióticos (HILL, 2020).

Desta forma, novas terapias para as necessidades individuais dos pacientes são procuradas. Os metabólitos da microbiota não exigem o trabalho com organismos vivos, e dentre estes metabólitos, moléculas lipídicas são extremamente promissoras como reguladores de diversos mecanismos de sinalização celular.

3 JUSTIFICATIVA

O transplante fecal tem se demonstrado eficaz para o tratamento de diversas patologias, como por exemplo síndrome metabólica e desordens neurológicas. Entretanto, a transferência de organismos vivos patogênicos, principalmente bactérias, limita sua utilização terapêutica. Assim, o estudo de metabólitos da microbiota intestinal pode oferecer uma nova estratégia terapêutica para auxiliar no tratamento de diversas doenças. Ainda, a classe lipídica parece ser a de maior impacto na regulação de diversas vias de sinalização celular, incluindo a via da inflamação. Portanto, estudo dos produtos lipídicos do metabolismo da comunidade microbiológica intestinal e seus constituintes são áreas promissoras para investigação detalhada.

4 OBJETIVOS

4.1 Objetivo Geral

Objetiva-se realizar uma revisão da literatura resultando em um artigo de opinião visto o impacto dos metabólitos lipídicos da microbiota no hospedeiro humano.

4.2 Objetivos Específicos:

- Identificar na literatura lipídios que tenham influência sobre a microbiota e consequentemente sobre o hospedeiro;
- Descrever interações farmacodinâmicas entre lipídios de microbiota e o hospedeiro;
- Discutir desfechos fenotípicos associados à microbiota.
- Indicar possíveis alvos terapêuticos e farmacológicos com base no conhecimento atual.

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CAPÍTULO 2 – ARTIGO CIENTÍFICO

Role Of Intestinal Microbiota Lipids in Phenotypic Outcome and Therapeutic Perspectives

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Abstract: Fecal transplantation has been shown to be effective for the treatment of various pathologies, such as metabolic syndrome and neurological disorders. However, the transfer of pathogenic living organisms, mainly bacteria, limits their therapeutic use. Thus, the study of metabolites of the intestinal microbiota may offer a new therapeutic strategy to assist in the treatment of various diseases. Furthermore, lipids seem to have the greatest impact on the regulation of several cell signaling pathways, including the pathway of inflammation. Therefore, study of lipid metabolites of the intestinal microbiological community and its constituents are promising areas for detailed investigation.

Keywords: Microbiota; Lipids; Diet; Feces; Metabolites; Therapeutic.

1 Introduction

In the 70s, it was estimated that 90% of cells in the human body weren't human's, but belong to the population of microscopic organisms that inhabit it [1]. Current sources estimate that the ratio of the number of human cells and bacterial cells is close to 1:1 [2]. Whatever the actual proportion, the influence of microorganisms on the human body is notorious and relevant to the health of its host. Bacteria, fungi, viruses and archaea are distributed in various organs and surfaces, such as skin, respiratory, reproductive and gastrointestinal tracts, in a symbiotic relationship, in which both parts are mutually [3]. This community of microorganisms is called microbiota. The microbiota is considered as an organ of its own [3], since it is composed of different cell lines that communicate with each other; consumes, stores, and redistributes energy; and has metabolic functions. Therefore, the microbiota is essential for the physiological maintenance of the organism.

At birth, the intestinal tract of the unborn child is sterile with bacterial colonization beginning in the first days of life [4]. The microbiota is an organ with great plasticity and adaptability; therefore, each individual develops a unique bacterial composition [5]. The composition of the microbiota is dependent on environmental factors such as host diet, age and use of antibiotics [6]. The population of microbiota varies between different parts of the intestine, with the colon containing the highest variety and overall amount of bacteria [7].

The gastrointestinal tract has a rich microbiota, with a wide variation in the number and species of microorganisms, mainly bacteria. It is estimated that between 15-35,000 species of bacteria colonize the intestine of an adult [8], with a majority belonging to the phyla Firmicutes and Bacteroidetes [9]. A comparative study between the microbiota of children from a rural African community and western Europe revealed an increased presence of Bacteroidetes versus an abundance of Firmicutes bacteria, respectively, giving its cultural diet setting. European children tend to have a high fat diet, with animal protein and low in fiber. As for African

children, their diet tend to be low in fat and animal protein; and rich in starch, fiber and polysaccharides [10]. This study highlights that both genera are two of the most prevalent in the gut and their colonization pattern is closely related to diet composition.

Microbiota bacteria are responsible for several metabolic functions, such as energy capture through carbohydrate degradation, polysaccharide fermentation, regulation of bile acid and choline metabolism; in addition to regulation of intestinal permeability and inflammation of peripheral tissues [11]. A healthy microbiota has been associated with an abundance of bacteria belonging to the genera *Bacteroides*, *Prevotella* and *Ruminococcus* [12].

The metabolism of the microbiological community is intricately linked with its host, contributing to several human metabolic pathways. In general, the intestinal microbiota performs functions related to the regulation of energy storage, protection against damage to the intestinal epithelium and stimulation of angiogenesis [13]. The commensal organisms influence the absorption of nutrients, promote protection against pathogens, metabolize drugs and xenobiotics, contribute to modulation of the immune system and provide the integrity of the intestinal environment and its structure [6]. Additionally, gut microbiota can impact behavior through the gut-brain axis, as extensively discussed in some other reviews [14–16].

Intestinal bacteria rely on the host's diet for survival. Bacteria often utilize carbohydrates, glycoproteins and other macromolecules derived from the diet as energy sources. Complex polysaccharides derived from plant cells and resistant starches, for example, are not digestible by the host’s enzymatic framework. Yet, these specific macromolecules are catabolized by enzymes within microorganisms of the gut, transforming them into absorbable particles such as vitamins and short-chain fatty acids, which contribute to the host’s nutritional uptake [11]. The fermentation pattern and, consequently, the metabolites to be excreted, depend on the composition and diversity of microorganisms of the microbiota [17]. However, the microbiota may present imbalances due to environmental changes.

The bacteria of the phylum Firmicutes and Bacteroidetes are predominant in the microbiota of most individuals, and the proportion between these bacteria has been associated with a predisposition to various diseases, especially obesity [18]. The example of the phylum Firmicutes and Bacteroidetes shows that the unbalance between these hegemonic groups can lead to a pathological state. This unbalance is called dysbiosis. Dysbiosis is caused by a population imbalance in the most common intestinal bacterial phyla and has been associated with phenotypical changes, such as infectious, inflammatory, and metabolic diseases, such as obesity [19–21]. Recent research done by Ren Z, et al., found by sequencing 16S rRNA gene from fecal and tongue-coating samples, that patients with COVID-19 present altered oral and gut microbiota as well as altered lipid profile, compared to a control population [22]. Dysbiosis can be established through factors such as diet modulation, intestinal infection, host genetics, as well as environmental factors [23]. Le Chatelier, et al., identified through quantitative metagenomics the characteristics that differentiate the microbiota according to its genetic variability and its implications on health and disease, in a recent study [24].

In Le Chatelier's study, metagenomic microbiota analysis of non-obese and obese individuals demonstrated that the genetically depleted microbiota favors inflammatory conditions due to factors such as: reduction of butyrate-producing bacteria, increased mucus degradation, reduction in hydrogen and methanol production potential, increase in pathogenic species (such as species from *Campylobacter* and *Shigella* genera), and increased peroxidases [24]. Among the diseases most associated with chronic inflammatory conditions are the inflammatory bowel syndromes, such as Crohn's disease and ulcerative colitis; obesity and even asthma [25].

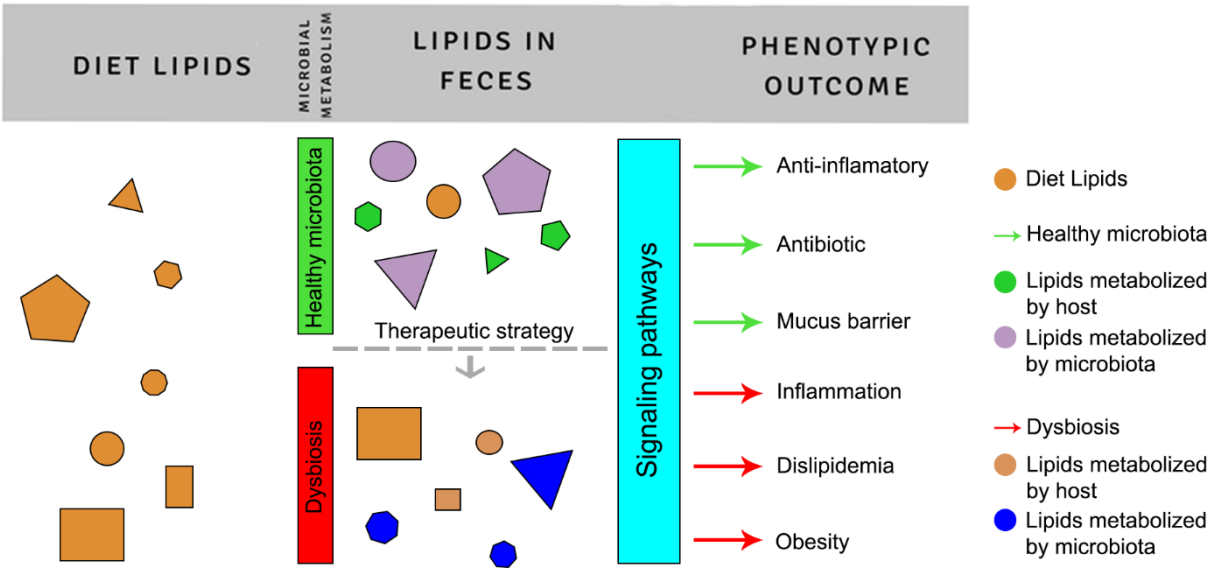

Fig. 1. Therapeutic strategy based on microbiota's metabolites

Graphical abstract from lipids in feces regulating phenotypic outcome. Lipids derived from the diet are metabolized by host's microbiota. Lipidic metabolites can activate different signaling pathways, that can lead to beneficial outcomes for the host or potentially favor diseases. The possibility of utilizing lipidic extracts from healthy donors' feces, represents a new therapeutic strategy.

2 Role of lipids in human metabolic pathways

Modification of a host's microbiota will indirectly alter the profile of their uptaken metabolites [26]. In the last decade, research has sought to identify the metabolites that have a direct influence on the individual's homeostasis and health status [27]. Some examples of metabolites are amino acids, polysaccharides, vitamins and lipids, such as short and long-chain fatty acids and bile acids [28].

Lipid molecules are among the metabolites of the intestinal microbiota that participate in the regulation of several signaling pathways of cell metabolism, acting as substrates for membrane and nuclear receptors [29,30]. The action of some lipid metabolites from the

intestinal microbiota, such as short-chain fatty acids (SCFA), has already been widely explored [31]; however, their therapeutic relevance has yet to be fully characterized.

Lipids are hydrophobic or, in some cases, amphiphilic biological molecules that are fundamental for the maintenance of human physiology. They can perform varied functions, such as energy storage, structural composition and both intercellular and intracellular biochemical signaling [32]. Literature shows that lipid molecules are closely involved with inflammatory processes and their regulation is, therefore, associated with the pathophysiology of several diseases of inflammatory nature [33]. Lipidomic analysis has expanded knowledge about the specific functions of lipids in biological systems and their contributions to signaling cascades. In the pathological context, lipidomic analysis is a valuable and innovative instrument for diagnostic prediction and therapeutic interventions [30,34].

The recent interest of the scientific community in microbiota has raised questions about the possible implications of metabolites from microbiota on the health of an individual. A review by J. Nicholson, et al., [35] discusses the importance of microbiota metabolites, including lipids, and their correlation with their metabolic functions of the host.

The characterization of lipid metabolites, produced by microbiota, is a promising area of study. As these metabolites participate in several metabolic pathways; their role in maintaining host homeostasis remains indispensable. Therefore, alterations related to lipid molecules are intertwined with the etiology of several diseases. Following are some of the most abundant and relevant lipids found within the gut, and the predominant bacteria genera that corroborate with a host's health and disease predisposition by way of these lipid metabolites.

In this work we categorized the lipids by the method of extraction, bile acids, SCFA and the last group as positively and negatively charged since they acquire charge during ionization in mass spectrometry.

2.1 Short Chain Fatty Acids (SCFA)

Short-chain fatty acids (SCFA) are the most elucidated microbiota metabolites. SCFA are fatty acids that have less than 6 carbons, being acetate (C2), propionate (C3), and butyrate (C4) the most abundant ones. Valerate (C5) and Caproate (C6) are not exclusively synthesized by the microbiota and are usually ingested with the diet [36]. SCFA are produced through complex carbohydrate fibers or non-digestible proteins and peptides present in the diet of the host that reach the colon without being absorbed or digested by mammals' enzymes. Bacteria located mostly in the colon promote fermentation of these substrates with carbohydrate-actived enzymes forming SCFA [37]. The type and amount of SCFA produced depends on factors such as transit time of the kilo in the intestine, the amount and type of bacteria of the microbiota, in addition to the dietary composition [38]. Also, it has been shown that the production of SCFA by Firmicutes and Bacteroidetes can be impacted by pH variations in the gastrointestinal tract. Therefore, Bacteroidetes fermentation occurs mostly in the distal colon, where the pH is about 6.3, yet the fermentation of Firmicutes often occurs in the proximal colon, where the pH is slightly lower [39].

SCFA's have a critical role in energy metabolism. When absorbed, they can be used as an energy source and as substrates for lipogenesis, gluconeogenesis, and cholesterol synthesis. Among other applications that are being elucidated, SCFA's can act as inflammation modulators, influence the composition of the microflora, act as vasodilators improving intestinal motility and contribute to mucosal integrity [40]. Thus, the type and quantity of SCFA can influence the development of an obese phenotype.

SCFAs are thought to act by two main mechanisms: G-protein coupled receptors (GPCR) activation and histone deacetylase (HDAC) inhibition [41].

GPCRs are present in different tissues. Propionate and butyrate bind to GPCR41 and GPCR43, receptors usually expressed in adipocytes, immune cells and enteroendocrine L cells.

Acetate binds primarily to GPCR43, present in gut epithelium and fetal membrane as well. This receptor, when activated, suppresses insulin signaling that would contribute to fat accumulation [42]. Butyrate also activates the receptor GPR109a, also known as hydroxycarboxylic acid receptor 2 (HCA2), that revealed anti-inflammatory responses when activated in disease contexts like diabetes, obesity, colitis, sepsis and Alzheimer's Disease [43]. An antitumor effect was reported with the activation of HCA2 by butyrate in malignant cells from the colon [44].

An increase of bacterial fermenters in the gut (dysbiosis) can lead to an augmented SCFA production due to an increase in the capacity of energy harvest [45]. GPCR41, when activated, stimulates the expression of the hormone leptin in adipocytes, stimulating adipogenesis [46]. These findings demonstrate that SCFA can be related to the onset of obesity in the context of dysbiotic scenarios.

A study in mice showed that a high fat diet increased GPCR43 expression in adipose tissue and that SCFA seems to increase peroxisome proliferator-activated receptor (PPAR) expression [46]. PPAR is a family of nuclear receptors that are located in many tissues and modulate the immune system [47] and energy metabolism [48]. Microbiota's metabolites like SCFA, PUFA (polyunsaturated fatty acids) and other fatty acids, can travel through systemic circulation and act as PPAR ligands in the liver, adipose tissue, blood vessels, heart, gastrointestinal tract, intestinal epithelium and immune cells that impact host inflammatory responses, energy metabolism and vascular homeostasis [48,49].

SCFA's can also mediate immune regulation promoting gene activation through inhibition of histone deacetylases (HDACs) [41]. Butyrate and propionate have the ability to inhibit lysine and histone deacetylase enzymes while butyrate metabolites stimulate acetyltransferases [50]. Both mechanisms increase histone acetylation and regulate gene transcription, decreasing NF-kB activity, and consequently, reducing production of IL-6, IL-8 and TNF$\boldsymbol{\alpha}$ [41].

Several studies have shown favorable outcomes to dietary supplementation of resistant fibers that favor the production of SCFA, causing changes in phenotypes related to obesity [51], colorectal cancer [52], diabetes [53], among other disorders.

2.2 Bile Acids

Bile acids (BA) are lipids produced in the liver derived from cholesterol. Bile acids have detergent action and are excreted by the gallbladder in the duodenum, emulsifying fat present in the diet [54],], facilitating digestion. However, their function in the body is not restricted to digestion alone. Primary bile acids (cholic acid and chenodeoxycholic acid) are conjugated with taurine or glycine before being stored in the gallbladder [55]. In the small intestine more than 90% of BAs are reabsorbed and return to the liver by enterohepatic circulation. However, around 5% to 10% of them continue to the colon, where they are modified by the local microbiota [56].

Bile salt hydrolases are enzymes that mediates the deconjugation of primary BA and are distributed mostly between the phylum *Firmicutes* (30%), *Bacteroidetes* (14.4%) and *Actinobacteria* (8.9%) [57]. Within these phyla, bacteria of the genera Bacteroides, Eubacterium, and Clostridium are known to have bile salt hydrolases and hydroxysteroid dehydrogenases: enzymes that promote the deconjugation of taurine and glycine and hydrolysis enabling the formation of secondary bile acids like deoxycholic acid (DCA) and lithocholic acid (LCA) [56]. Secondary bile acids are more lipophilic and are, therefore, reabsorbed by the intestinal epithelium and enter the circulation [56].

Primary and secondary bile acids bind to hormonal nuclear receptors present in various cell lines, such as enterocytes, hepatocytes, and adipocytes, called Farnesoid X receptors (FXR) [58]. The activation of FXR implies the regulation of genes associated with the synthesis and transport of BA, carbohydrate metabolism and regulation of intestinal innate immunity [59].

Through the activation of FXR, microbiota metabolites can reduce lipogenesis, increase the oxidation of fatty acids and promote removal of triglycerides in plasma, thus reducing the risk of developing metabolic diseases [60].

Secondary BAs like DCA and LCA also activate the G-protein receptor TGR5, which is widely expressed in different cell types. In macrophages, it inhibits secretion of TNF-α, IL-1β and IL-6 [61] producing an anti-inflammatory effect. Reduction of secondary bile acids occurs in dysbiotic scenarios since it's bacterial-dependent, contributing to the inflammatory picture [62]. In adipocytes and myocytes, secondary BAs promote energy expenditure [63], preventing obesity and resistance to insulin.

Bile acids have the potential to promote oxidative stress and damage to membranes and DNA. This gives them antibacterial properties against pathogens such as *Clostridium difficile* [64]. Therefore, bile acids can be considered important regulators of the microbiota population. Another current hypothesis for *C. difficile* management by BAs is that, unlike primary bile acids, secondary bile acids may inhibit spores' germination. A study by Weingarten, et. al, revealed that fecal microbiota transplant (FMT) increased secondary bile acid levels in feces samples from recurrent *C. difficile* patients [65].

The metabolism of bile acids plays an important physiological role. However, depending on the amount and type of secondary bile acids produced; BA's may impact the body in a beneficial way or contribute to pathological conditions. Changes involving the metabolism of bile acids were associated with IBD and metabolic diseases such as diabetes, obesity [66] and colorectal cancer [67].

2.3 Positive and negatively charged lipids

2.3.1 Phospholipids

Lipids classified as phospholipids include: cardiolipin (CL), phosphatidylcholine (PC), phosphatic acid (PA), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylinositol (PI) and phosphatidylserine (PS). Phospholipids are important for structure, permeability and fluidity of membranes and also proteins, receptors and ion channels [68]. The most abundant phospholipids in eukaryotic cells are phosphatidylcholine (PC) and phosphatidylethanolamine (PE) [69]. Conversely, few species of bacteria contain PC's in their membrane structures, but most have PE as major components of the cell, followed by phosphatidylglycerol and cardolipin [69].

CL has a crucial role in metabolic function of cellular respiration for being a structural component of mitochondrial membrane. CL's are important molecules that participate in processes like cell death, mitophagy and innate immunity and can be found in diverse tissues such as the brain, heart and muscles [70]. Additionally, CL has been shown to inhibit tumor necrosis in cells by inhibiting the LPS-induced TNF-α [71], and is an antagonist of TLR4. This lipid, and other negatively charged phospholipids, can also inhibit lipopolysaccharide (LPS) inflammatory effects from gram-negative bacteria of the microbiota, maintaining homeostasis [71].

PC can be synthesized in the liver or ingested in the diet [72]. This lipid is present in animal-derived food – including milk, eggs, red meat, fish, and others – and is the major source of choline, an essential nutrient [73]. PC plays a role in the formation of trymethylamine-N-oxide (TMAO), that can increase the risk of cardiovascular diseases [73]. Consumption restrictions of PC in the diet may modulate the microbiota reducing plasma levels of TMAO [74]. However, a study by Yu, et. al, [75] showed that the consumption of polyene phosphatidylcholine, a drug used to treat liver steatosis, could regulate the gut microbiota without altering TMAO levels, increase SCFA concentration and attenuate lipopolysaccharide (LPS) levels.

PA is an important metabolite involved in the synthesis of membranes, but it also has a significant role in nervous system signaling [76]. It can activate the mTOR pathway via an ERK pathway [77]. There is no known association between PE and the microbiota.

PE is a lipid present in the inner leaflet of membranes, especially mitochondria, [78] and is produced by two different pathways: CDP-ethanolamine in the endoplasmatic reticulum or the PS pathway in mitochondria [79]. It can participate in different metabolic processes such as cell division, cell fusion, coagulation, or apoptosis [80–83]. Microbiota can affect the amount of PE produced in the intestine. In a 2021 study, [84] Liebisch, et. al, demonstrated that germ-free mice present higher levels of PE than specific pathogen-free mice. The proportions and balance of PE to PC seem to have important health consequences. The PE:PC ratio has been shown to contribute to steatogenesis and inflammation [85].

PS is known as a vital apoptosis signaling molecule, but it has a variety of cell functions. Although it is not exposed in the outer membrane of healthy cells, PS is involved in cell signaling, synthesis of mitochondrial PE, blood coagulation, immunosuppression, among other functions [86], but no correlation with the microbiota was found.

In short, the available literature suggests that the human gut microbiome may be associated with phospholipids such as CL, PE, PC and PG, reaffirming the contribution of gut bacteria in metabolic lipid pathways.

2.3.2 Sphingolipids

Sphingolipids are structural cell lipids that serve as important signaling molecules in eukaryotic and prokaryotic organisms. Sphingolipid molecules consist of one of three amino acids — serine, alanine, or glycine — in union with palmitoil-CoA. These molecules can be transformed from ceramides, the structural precursors, into more complex sphingolipids, such as sphingomyelin, glycosphingolipids, sphingomyelin, ceramide-1-phosphate (C1P) or S1P

[87]. These lipids are involved in key cellular processes like apoptosis, senescence, cell differentiation and inflammation [87], and in altered levels of availability have been shown to modulate host gut microbiota complexity.

Studies of dietary supplementation of sphingolipids have shown promising results for the treatment of dyslipidemia. In a study with mice modeling dyslipidemia, sphingomyelin supplementation caused a decrease of lipid and cholesterol absorption [88]. Furthermore, mice fed a high-fat diet with sphingolipid supplementation exhibited a reduction in triglycerides level and a downregulation of hepatic PPARg-related genes, [89] while some others presented alterations in their microbiota's population [88].

Certain groups of anaerobic bacteria have sphingolipids as structural components of their membranes, especially those belonging to the genus Bacteroides [90]. Bacteroidetes metabolites, associated with the sphingolipid class, modulate natural killer (NKT) T cell [91] recruitment during inflammatory processes and influence B cell differentiation [92].

2.3.3 Lysophospholipids

Lysophospholipids (LPL) are bioactive fragments of phospholipids. Lysophosphaditylcholine (LPC), lysophosphatidilinositol (LPI), and their byproduct lysophosphatidic acid (LPA), are the most biologically active lysophospholipids [93]. LPL's biological effect is mostly mediated by various types of GPCRs [94]

LPC and LPA can modulate immune responses by activating inflammatory pathways, stimulating pro-inflammatory mediators as well as acting as chemoattractants [95]. A plasmatic LPL elevation has been associated with some chronic inflammatory diseases, such as obesity [96], diabetes [97], atherosclerosis, rheumatoid arthritis [98], and even cancer [99]. Since the increase of LPC levels is correlated with disease development, one might hypothesize that microorganisms from the microbiota contribute to the inflammatory condition by acting as an

alternative source of phospholipids and consequently LPL [100]. Thus, quantifying the abundance of lysophospholipids can be an important disease biomarker, presenting itself as an early sign of pathologies. A study by Fuchs, et. al, indicated that PC/LPC ratio, in plasma, can be used as a severity biomarker of rheumatoid arthritis and a tracker of a treatment's efficacy [98].

3 Lipid metabolites of main bacterial phylum

The healthy human gut microbiome is composed, mostly, of bacteria from the Bacteroidetes and Firmicutes phylum followed by Actinobacteria [12]. A gut microbiome populated with a majority of bacteria from the Bacteroidetes phylum is usually correlated with the lean phenotype, while Firmicutes abundance is mostly associated with obese phenotypes. Identifying the metabolites produced by bacteria of these phyla is critical to understanding host-microbiota relations.

3.1 Firmicutes

An analysis of the diversity of the human microbiome revealed that 95% of the Firmicutes belong to the Clostridia class [13]. The pathogenicity of some species of the genus *Clostridium* is extensively researched and well-known, mostly represented by *Clostridium difficile*; however, it is important to discuss the influence of the *Clostridium* genus on host homeostasis as well as their benefits.

Most *Clostridium* species are well-known as butyrate-producing bacteria [13]. Species like *Clostridium butyricum* are used, clinically, as a probiotic to treat intestinal diseases, including diarrhea and IBD [101]. The same species has shown anticarcinogenic potential in randomized clinical trials when used as a probiotic treatment for dysbiosis related to colorectal cancer [102]. However, it is important to note that although some *Clostridium* bacteria

metabolites can have tumor suppressing effects; other species from the same genus can have the opposite effect. Glycolithocholate, a secondary bile acid produced by *Clostridium scindens*, causes a decrease in tumor suppressing NKT cells in a mouse's liver [103]. Although *Clostridium* lipid metabolites have, sometimes, ambiguous effects on the host, there is evidence to support the need for balance and variability between species to maintain healthier microbiota.

The famous species *Lactobacillus,* is classified under the Firmicutes phylum and was the first bacterial species recognized as a relevant part of the human body [104]. The Lactobacillaceae family has an intricate relationship with dietary polyunsaturated fatty acids (PUFA), namely linoleic acid (LA). PUFAs, and their metabolites, are known to have essential roles in brain function [105] and modulation of inflammation [106].

Though a high fat diet (HFD) is mostly associated with an increase of Firmicutes and decrease of Bacteroidetes, the supplementation of LA showed the inverse effect, with the exception of the Lactobacillaceae family which was augmented [107]. Species like *Lactobacillus salivarius, Lactobacillus gasseri, Lactobacillus acidophilus* and *Lactobacillus johnsonii* produce 10-hydroxy-cis-12-octadecenoic acid (HYA), a gut microbiota lipid metabolite derived from LA [107]. Evidence suggests that HYA could enhance intestinal barrier function preventing the development of colitis via GPR40 activation [108]. Also, supplementation of HYA in mice exhibiting HFD-induced obesity promoted insulin sensitivity, reduction of cholesterol and glucose levels as well as appetite suppression [107]. Therefore, HYA supplementation presents itself to be a promising therapy for obesity and metabolic diseases.

3.2 Bacteroidetes

An extensive part of gut microbiota is composed of bacteria from the Bacteroidetes phylum, such as *Bacteroides* and *Prevotella spp* [109]. Bacteroidetes are one of the few

bacterial phylums that produce sphingolipid [90,110]. Sphingolipids like ceramides, glycosphingolipids and sphingosine-1-phosphate, are structural components of Bacteroidetes phylum membranes [111] and seem to be indispensable for bacterial survival under stress [112].

Evidence shows that bacterial sphingolipids can modulate the host's immune system. The absence of *Bacteroides*-derived sphingolipid ceramide phosphoethanolamine (CerPE) is associated with epithelial gut inflammation common in IBD [113]. It has been shown that *Bacteroides*-derived sphingolipids can influence the immune system by inhibiting proliferation and activation of in-variant NKTs, thus decreasing proinflammatory responses. A study by Eric M. Brown, et. al, [113]] found a correlation between bacterial sphingolipid deficiency and inflammatory bowel diseases, bolstering the protagonism of lipid metabolites in relation to the health status of its host.

The effect of *B. fragilis* glycosphingolipids over iNKT cells demonstrates that these lipid metabolites can be used to treat diseases such as auto immune and allergic disorders mediated by iNKT cells [91].

3.3 Actinobacteria

Bifidobacteria are one of the first bacterial species to initiate colonization of the human gut. During the first year of life, *Bifidobacterium* are the most prominent genus of the colon microbiota, decaying in abundance during the following years [114]. *Bifidobacterium* species are known to produce short-chain fatty acids (SCFA), derived from fermentation of several carbohydrates (plant and human-derived) [115]. Its most abundant metabolite, acetate, activates GPCR43 receptors in adipocytes, suppressing insulin signalling [116]. Previous studies have also demonstrated that acetate derived from Bifidobacteria improves intestinal defense against pathogenic bacteria [117]. The metabolic implications of acetate in the organism have supported the use of bifidobacteria strains as probiotics. The presence of selected strains of

Bifidobacterium have been associated with numerous health benefits, such as treatment of diarrhea, relief of lactose intolerance and constipation, resistance to bacterial infections and even prevention of cancer [118].

The use of bifidobacteria as probiotics show promising results in metabolic disorder prevention. A study by Aoki, et. al, showed that *B. animalis ssp. lactis* GCL2505 used as a probiotic can prevent metabolic disorders, improve glucose tolerance and lead to suppression of visceral fat accumulation [119].

A study in mice revealed that *Bifidobacterium longum subsp. Longum* supplementation (BL21) was associated with an alteration in glycerophospholipid metabolism with augmented PS, PE and PC concentrations [120]. Wu, et. al, describes that the increase of these membrane lipids can change the fluidity and permeability of membranes, improving its adaptation to external stress. It also suggests that PS may represent a potential biomarker of BL21's hepatoprotective effect against obesity [120].

Thus, lipid metabolites such as acetate, PS, PE, and PC from the *Bifidobacterium* genus have shown positive effects on human health.

4 Past and future microbiota-based therapies

The proposition of the positive influence of microorganisms on the health of an individual was made by Elie Metchnikof, who describes for the first time the beneficial effects that bacteria of the Lactobacillus family could provide [104]. The revolutionary proposal gave rise to probiotics and prebiotics, which are living microorganisms and non-digestible food components, respectively, that reestablish the balance of the microbiota by increasing the population of beneficial microorganismss [121].

Prebiotics and probiotics have been used for years for both prevention and treatment of pathological situations, such as lactose intolerance, intestinal tract infections, constipation,

allergies, even cancer and others [122]. Although more promising, robust and randomized clinical trials are still needed to affirm the mechanisms of action and efficacy of their treatments. For example, treatment outcome is very dependent on the strain used, in the case of probiotics, and the characteristics inherent to the host treated and microbial ecosystem integration, in the case of prebiotics [123].

Since Metchnikof's discovery, much has been unraveled about the complexity of the microbiome and its interactions with the host, mostly with recent multi-omics studies. Recent data showed that richness and diversity of the microbiota is a crucial health indicator, and dysbiosis can be a pathological sign or cause of diseases. In this context, therapy based on FMT is currently used for treatment of recurrent or refractory *Clostridium difficile* infection [124], in order to restore a normal intestinal microbiome. Microbiota transplantation sources microorganisms from a healthy donor's fecal sample, which can be performed by endoscopy, colonoscopy, retention enema or orally through capsules [125].

Phenotypes associated with diseases have been shown to be transmissible through microbiota transfer. In 2006, Turnbaugh and colleagues performed a microbiota transplant in germ-free mice using lean and obese donors. The mice colonized with microbiome from obese donors showed more effective energy harvest and, consequently, gained twice as much fat as those who received the microbiota from lean mice [126]. Therefore, the use of FMT is being investigated for the treatment of various disturbances and diseases such as obesity [127], IBD [128], Crohn's disease [129], systemic sclerosis [130], but additional clinical trials are needed.

Despite the great therapeutic potential of the intestinal microbiota, as mentioned, fecal transplants may also contain pathogenic living organisms that could be lethal to the receiver. Patients undergoing transplantation should be monitored after therapy due to the possible manifestation of adverse effects present in 28.5% of cases [131] such as infection by pathogens that can lead to death. Recently, the FDA (Food and Drug Administration), the US Federal

Agency of the Department of Health and Human Services, released a safety alert and suspended several procedures that used fecal transplant therapy due to the death of a patient, and another who became seriously ill [132]. Analysis of stool samples from the donor showed the presence of *Escherichia coli* resistant to antibiotics [133].

Application of therapies involving microbiota metabolites can be advantageous to avoid the possible pathogenicity associated with the accidental transplant of unwanted living microorganisms. The modulation of the lipid composition of cell membranes has been studied as a possible therapeutic target for the treatment of several diseases, such as obesity, diabetes, hypercholesterolemia, and other metabolic syndromes; and even cardiovascular and neurodegenerative diseases, as indicated by the review by Pablo V. Scribá, et. al [134]. Table 1 shows some of the researched lipid-based treatment.

Table 1. Lipid based treatment perspectives

Abbreviations: MAP - mitogen-activated protein kinase, NF-kB – nuclear factor kappa B, NKT – natural killer T and PPAR – peroxisome proliferator-activated receptor, SCFA – short-chain fatty acid, TNF-α - Tumor necrosis factor alpha.

Lipid Class	Lipid	Therapeutic opportunity	Mechanism	Reference
SCFA	Butyrate	Cancer	Anti-tumor effects promoting apoptosis and differentiation in epithelial cells	[135]
		Crohn's disease	Inhibits the NF-kB pathway decreasing inflammation	[136]
		Diabetes	Inhibition of insulin resistance in a high fat diet preventing obesity in mice	[137]
	Propionate and Butyrate	Obesity	Reduces food intake	[138]
Bile Acids	Lithocholic acid	Cancer	Control of NKT cells in liver cancer	[103]
	Deoxycholic acid and lithocholic acid	Clostridium difficile infection	Enhances antibiotic action of C. scindens and C. sordellii metabolites in C. difficile infection	[139]

Phospholipids	Phosphatidylcholine	Ulcerative colitis	Increases hydrophobicity on the luminal surface of the GI-tract, inhibits actin nucleation, TNF-α mediated NF-κB nuclear translocation, MAP kinase activation and pro-inflammatory cytokine expression	[140]
Sphingolipids	Sphingomyelin	Hepatic steatosis	Reduction of hepatic steatosis and PPAR genes correlated when used as diet supplement	[141]
	Ceramide	Cancer	Prominent drugs that induce tumor death via apoptosis	[142]
Fatty acids	Omega 3	Neuropsychiatric disorders	Omega 3 supplement for prevention of neurological diseases	[143]

Thus, although it may seem odd suggesting lipid therapies for lipid metabolic disorders, the study of lipid metabolites from the intestinal microbiota shows promising results as discussed in many metabolic disorders, including those where FMT is being considered. Therefore, identification of new lipid molecules and their therapeutic functions can serve as a path towards safer interventions.

Microbiome-based therapies could also be the way for a more personalized medicine. Each individual has its own microbial ecosystem, tailored through time, environmental and genetic factors, thus hindering clinical research analysis with many variables. Identifying dysbiotic scenarios, and specific shortages or changes of key metabolites in plasma and stool, may be the first step to provide specific supplementation or treatment. Diet has the most direct and prolonged impact on the microbiota's composition and should be the main target of health care, considering the tools of personalized nutrition. Nevertheless, personalized medicine could be used as the first line of treatment for a robust initial response being accompanied by a growing change in dietary habits.

5 Conclusions and perspective

Recent evidence points to the crucial yet complex role of lipids in many metabolic pathways. Advances in lipidomics technology opens new ways to understand lipid homeostasis. Systematic characterization of microbiota metabolites and their individual impacts on host homeostasis is a relatively new area of study. Though there is yet much to uncover, the potential for discovery of novel diagnostic strategies, drugs and therapies based on microbiota metabolites brings hope for treatment of complicated yet currently common health issues like obesity and cancer.

New therapies for the individual needs of patients are sought. Metabolites of the microbiota do not require work with living organisms, and among these metabolites, lipid molecules are extremely promising as regulators of various signaling mechanisms in the cell, mostly correlated with inflammation. Lipids such as SCFA, PUFA, secondary bile acids, sphingolipids, phospholipids and lysophospholipids, derived from microbiota's metabolic pathways, have an impact on hosts' health. It is suggested that future characterization of pathologies include lipidomic and metabolomic assays in order to uncover health and disease biomarkers and new therapeutic targets.

As shown in this review, lipids are a relevant type of metabolite that also influence health or disease conditions. In this context, could lipidic extracts from a healthy donor's stool also be used as a therapy to produce a healthier phenotype in acceptors? Clinical research is needed to test this hypothesis.

Acknowledgments

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of interest

The authors do not have any conflicts of interest to report.

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ANEXOS

ANEXO A: Normas de formatação do periódico "*Progress in Lipid Research*"

Article structure

Subdivision - numbered sections

Divide your article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Use this numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Title
The title should be short and enticing (ideally eight words or fewer), and should not contain abbreviations. Please feel free to suggest your own title.

Abstract
All reviews should be prefaced by a summary of recent advances of 200-250 words. The summary is important: it should contain sufficient information for the reader to be able to appreciate the relevance of the full review when read alone. Summaries are used by abstracting services and many users of these services read only the summary. It should include background information and specific examples of recent advances, rather than promises that a particular subject will be discussed - the scope of the review should instead appear at the end of the introduction. References should not be included and abbreviations should be avoided as far as possible.

Introduction
The introduction should be accessible to a wide variety of scientists by avoiding the use of jargon and concepts

Main text or review
Use concise, logical subheadings to provide clear links between the different sections and guide the reader

Conclusions and perspective
The conclusions section should summarise the topics discussed and describe future directions, including the

Introduction
State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods
Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Theory/calculation
A Theory section should extend, not repeat, the background to the article already dealt with in the Introduction and lay the foundation for further work. In contrast, a Calculation section represents a practical development from a theoretical basis.

Results
Results should be clear and concise.

Discussion
This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions
The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices
If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Essential title page information

• ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
• ***Author names and affiliations.*** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
• ***Corresponding author.*** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. **Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.**
• ***Present/permanent address.*** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Highlights

Highlights are optional yet highly encouraged for this journal, as they increase the discoverability of your article via search engines. They consist of a short collection of bullet points that capture the novel results of your research as well as new methods that were used during the study (if any). Please have a look at the examples here: example Highlights.

Highlights should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

Keywords

Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Abbreviations
Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

Acknowledgements
Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Formatting of funding sources
List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, please include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Depositing Novel Lipid Structures in LIPID MAPS Database:
Progress in Lipid Research recommends that authors of manuscripts deposit all novel lipid molecules for registration in the LIPID MAPS structure database prior to publication. This will be extremely beneficial in terms of (a): maintaining and expanding a comprehensive lipid database covering a wide variety of sources (e.g., mammals, plants, fungi, bacteria, marine organisms), (b): accurate classification of new lipid structures, (c): application of consistent nomenclature standards with regard to systematic names and abbreviations, and (d): consistent and unambiguous structural representation. The preferred method for depositing lipid structures is a Web-based registration system on the LIPID MAPS Web site that will enable authors to enter lipid structures and accompanying names, synonyms, references, and classification information. During the submission process, structures are validated for uniqueness using a search on the current database. The submitted structures are then stored in a private, temporary database where they are reviewed by LIPID MAPS bioinformatics staff prior to being classified, checked for correct nomenclature, and registered in the public LIPID MAPS structure database. Questions regarding the submission of structures should be directed to webmaster@lipidmaps.org.

Math formulae
Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Footnotes
Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors can build footnotes into the text, and this feature may be used. Otherwise, please indicate the position of footnotes in the text and list the footnotes themselves separately at the end of the article. Do not include footnotes in the Reference list.

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Image manipulation
Whilst it is accepted that authors sometimes need to manipulate images for clarity, manipulation for purposes of deception or fraud will be seen as scientific ethical abuse and will be dealt with accordingly. For graphical images, this journal is applying the following policy: no specific feature within an image may be enhanced, obscured, moved, removed, or introduced. Adjustments of brightness, contrast, or color balance are acceptable if and as long as they do not obscure or eliminate any information present in the original. Nonlinear adjustments (e.g. changes to gamma settings) must be disclosed in the figure legend.

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General points

• Make sure you use uniform lettering and sizing of your original artwork.
• Embed the used fonts if the application provides that option.
• Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, Symbol, or use fonts that look similar.
• Number the illustrations according to their sequence in the text.
• Use a logical naming convention for your artwork files.
• Provide captions to illustrations separately.
• Size the illustrations close to the desired dimensions of the published version.
• Submit each illustration as a separate file.
• Ensure that color images are accessible to all, including those with impaired color vision.

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Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):
EPS (or PDF): Vector drawings, embed all used fonts.
TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.
TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi.
TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.
Please do not:
• Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
• Supply files that are too low in resolution;
• Submit graphics that are disproportionately large for the content.

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Please make sure that artwork files are in an acceptable format (TIFF, EPS or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color on the Web (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. Color reproduction in print will be free of charge, provided the figure warrants reproduction in color and a reasonable number is submitted. Please clearly indicate your preference for color in print or on the Web only, to help us save unnecessary costs. For further information on the preparation of electronic artwork, please see https://www.elsevier.com/artworkinstructions Please note: Because of technical complications which can arise by converting color figures to "gray scale" (for the printed version should you not opt for color in print) please submit in addition usable black and white versions of all the color illustrations.

Figure captions
Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables

Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules and shading in table cells.

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Citation in text
Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

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As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

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This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

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Text: Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given.
List: Number the references (numbers in square brackets) in the list in the order in which they appear in the text.
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Reference to a journal publication with an article number:
[2] Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. Heliyon. 2018;19:e00205. https://doi.org/10.1016/j.heliyon.2018.e00205
Reference to a book:
[3] Strunk Jr W, White EB. The elements of style. 4th ed. New York: Longman; 2000.
Reference to a chapter in an edited book:
[4] Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, editors. Introduction to the electronic age, New York: E-Publishing Inc; 2009, p. 281–304.
Reference to a website:
[5] Cancer Research UK. Cancer statistics reports for the UK, http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/; 2003 [accessed 13 March

2003].
Reference to a dataset:
[dataset] [6] Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. https://doi.org/10.17632/xwj98nb39r.1.
Note shortened form for last page number. e.g., 51–9, and that for more than 6 authors the first 6 should be listed followed by 'et al.' For further details you are referred to 'Uniform Requirements for Manuscripts submitted to Biomedical Journals' (J Am Med Assoc 1997;277:927–34) (see also Samples of Formatted References).

Journal abbreviations source
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Include interactive data visualizations in your publication and let your readers interact and engage more closely with your research. Follow the instructions here to find out about available data visualization options and how to include them with your article.

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