UNIVERSIDADE DE BRASÍLIA
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MARIANA MARTINS GUIDA

ASSOCIAÇÃO ENTRE O SISTEMA ENDOCANABINOIDE E O SARS-COV-2: UMA REVISÃO DE ESCOPO

BRASÍLIA, 2023

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Orientador: Profa. Dra. Vivian da Silva Santos

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A todas as vítimas da COVID-19 que não puderam estar aqui para estas descobertas.

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RESUMO

Introdução: O sistema endocanabinoide, que desempenha um papel em vários processos biológicos, incluindo a regulação da função imune, do comportamento humano e do metabolismo, também está relacionado à modulação das funções celulares imunes e suas propriedades anti-inflamatórias foram estudadas em relação a doenças como diabetes, distúrbios cardiovasculares, câncer e doenças autoimunes. Especula-se que exista associação entre o sistema endocanabinoide e o coronavírusda síndrome respiratória aguda grave 2 (SARS-CoV-2) e compreender essa associação auxilia o entendimento de mecanismos do vírus e da inflamação, bem como alvos terapêuticos. **Metodologia:** Este estudo é uma revisão de escopo. O estudo foi realizado através da busca bibliográfica nas plataformas MEDLINE/PubMed e *Web of Science* usando termos de pesquisa específicos “COVID-19”, “Coronavirus”, “Endocannabinoid system” e “Cannabinoids” e operadores booleanos “AND” e “OR”. Aplicou-se critérios de inclusão e exclusão e os artigos selecionados foram analisados criticamente para sintetizar as descobertas e identificar lacunas na literatura. **Resultados:** Os 13 artigos selecionados analisaram o papel de substâncias endógenas e exógenas na mitigação do impacto do SARS-CoV-2, o vírus que causa a COVID-19. Os artigos foram divididos em três categorias: 1- antes da infecção (n= 3 artigos), 2- Durante a infecção (n= 7 artigos) e 3- COVID longa (n= 3 artigos). **Conclusões:** Considerando os achados obtidos por meio deste trabalho, é possível inferir que a COVID-19 é diretamente afetada pela ação do sistema endocanabinoide, determinando fatores como infectividade da doença, inflamação e recuperação. A fisiopatologia da COVID-19 também é um meio para compreender melhor o *sistema endocanabinoide expandido* e sua interação com o tradicional e bem conhecido sistema endocanabinoide.

Palavras-Chave: COVID-19; Sistema endocanabinoide; Sistema endocanabinoide expandido; COVID longa.

ABSTRACT

Introduction: The endocannabinoid system plays a role in several biological processes, such as regulation of immune function, human behavior, and metabolism. The endocannabinoid system is related to the modulation of immune cell functions and its anti-inflammatory properties have been studied in relation to diseases such as diabetes, cardiovascular disorders, cancer, and autoimmune diseases. It is speculated that there is an association between the endocannabinoid system and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and understanding this association helps understanding the mechanisms of the virus and inflammation, as well as therapeutic targets. **Methodology:** This study is a scope review. The study was carried out through a bibliographic search on the MEDLINE/PubMed and Web of Science platforms using specific search terms “COVID-19”, “Coronavirus”, “Endocannabinoid system” and “Cannabinoids” and Boolean operators “AND” and “OR”. Inclusion and exclusion criteria were applied, and selected articles were critically analyzed to synthesize findings and identify gaps in the literature. **Results:** The 13 selected articles analyzed the role of endogenous and exogenous substances in mitigating the impact of SARS-CoV-2, the virus that causes COVID-19. Articles were divided into three categories: 1- before infection (n= 3 articles), 2- During infection (n= 7 articles) and 3- long COVID (n= 3 articles). **Conclusions**: Considering the findings obtained through this work, it is possible to infer that COVID-19 is directly affected by the action of the endocannabinoid system, determining factors such as disease infectivity, inflammation, and recovery. The pathophysiology of COVID-19 is also a means to better understand the expanded endocannabinoid system and its interaction with the traditional and well-known endocannabinoid system.

Keywords:.COVID-19; Endocannabinoid system; Endocannabinoidome; Long COVID.

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS

2-AG: 2- araquidonilglicerol

AA: Ácido aracdônico

AC: Adenilil ciclase

ECA2: Enzima conversora de angiotensina 2

AEA: Anandamida

cAMP: Monofosfato cíclico de adenosina

CB1: Receptor endocanabinoide 1

CB2: Receptor endocanabinoide 2

CBD: Canabidiol

COVID-19: da sigla em inglês, Corona Virus Disease 2019

DAGL: Diacilglicerol lipase

FAAH: Amida hidrolase de ácidos graxos

GPR55: Receptor acoplado à proteína G 55

IFN-γ: Interferon gama

IFN-I: Interferon I

IL-2: Interleucina-2

IL-4: Interleucina- 4

IL-6: Interleucina-6

MAGL: Monoacilglicerol lipase

MAPK: Proteínas quinase ativadas por mitógeno

NAPE-PLD: N-acil fosfatidiletanolamina fosfolipase D-específica

NAT: N-acetiltransferase

PLC: Fosfolipase c

SARS-CoV-2: Coronavírus da síndrome respiratória aguda grave 2

SEC: Sistema endocanabinoide

THC: Δ9-tetrahidrocanabinol

TLR: Receptores toll-like

TNF-α: Fator de Necrose Tumral

SUMÁRIO

1. Introdução

Os avanços na medicina permitiram uma nova ênfase no sistema endocanabinoide e sua importância nos processos biológicos do corpo. Esse sistema é composto por: i) receptores canabinóide tipo 1 (CB1) e canabinóide tipo 2 (CB2); ii) seus agonistas endógenos conhecidos anandamida (AEA) e o 2-araquidonilglicerol (2-AG), bem como iii) enzimas responsáveis pela síntese e degradação de endocanabinoides (JOSHI; ONAIVI, 2019).

Os receptores CB1 e CB2 estão localizados sistema nervoso central (SNC), sistema nervoso periférico (SNP), órgãos, glândulas e células imunes exercendo funções neurológicas, metabólicas, comportamentais e imunológicas (JOSHI; ONAIVI, 2019). Eles são expressos de formas diferenciada no organismo, sendo o CB1 majoritariamente encontrado no sistema nervoso, enquanto o CB2 pode ser encontrado em sua maioria, mas não exclusivamente, perifericamente associado ao sistema imunológico (principalmente em linfócitos B e em macrófagos), sendo sua ativação relacionada a propriedades anti-inflamatórias (LU; MACKIE, 2021 e TANASESCU; CONSTANTINESCU, 2010)

Além do receptor CB2 estar fortemente associado ao sistema imunológico, os endocanabinoides AEA e 2-AG são compostos lipídicos derivados do ácido aracdônico e similares às prostaglandinas envolvidas nos processos de inflamação (FONSECA *et al*., 2004). De acordo com Klein *et al*. (2003), outra possível relação do sistema endocanabinoide com o sistema imunológico é a modulação das funções das células imunológicas por meio de sinalizações mediadas por CB1 e CB2.

Os mecanismos por detrás da imunomodulação desempenhada pelo sistema endocanabinoide e suas propriedades anti-inflamatórias ainda não estão totalmente elucidados, mas já há descrição na literatura sobre a possível atuação deste sob uma gama de doenças, como diabetes, desordens do sistema cardiovascular, câncer e doenças auto-imunes (LOWE *et al*., 2021).

De acordo com Tanasescu e Constantinescu (2010), os receptores endocanabinoides estão envolvidos no processo de *feedback* negativo do monofosfato cíclico de adenosina (cAMP), que por sua vez, é modulado pela enzima Adenilato Ciclase (AC). A atividade desses compostos está associada à ativação de linfócitos e com a transcrição de citocinas por macrófagos.

É importante citar que a mediação causada pelo sistema endocanabinoide

ocorre de forma que pode haver uma supressão das citocinas que potencializam a inflamação (TANASESCU; CONSTANTINESCU, 2010). Isto têm grande relevância quando associado à infecção pelo vírus do coronavírus da síndrome respiratória aguda grave 2 (SARS-CoV-2), o agente etiológico da *Corona Virus Disease 2019* (COVID-19), pois os casos mais graves têm sido associados com as chamadas “tempestade de citocinas” (EL BIALI *et al*., 2020).

Considerando a relação entre o sistema endocanabinoide e o sistema imunológico estabelecida na literatura científica vigente, é possível que haja uma correlação entre esse sistema e a infecção pelo vírus SARS-CoV-2. Nessa perspectiva, a elucidação dessa conexão pode auxiliar na compreensão dos mecanismos de infecção, inflamação e cura da doença.

2. Revisão Bibliográfica

2.1. Sistema Endocanabinoide

A história das plantas do gênero *Cannabis*, incluindo a mais popular, *Cannabis Sativa,* é milenar, passando pelos Tocarianos na Ásia Central, usos medicinais na China por imperadores de 2000 a.C. e, posteriormente, pelo Egito em 1500 a.C., pelas civilizações romanas em 23 d.C., e muitos outros relatos. (CROCQ, 2020). No entanto, foi somente em 1988 em que um receptor endógeno para as substâncias provenientes da Cannabis foi descrito na literatura (DEVANE *et al*., 1988).

O receptor que foi descrito foi o CB, mas hoje é de conhecimento geral que este, em conjunto com o CB2, são constituintes de um sistema endógeno de sinalização chamado de Sistema Endocanabinoide (SEC) (WANG; UEDA, 2009).

Tanto CB1 como CB2 são da superfamília de receptores acoplados à proteína G, receptores como este tem função de transduzir sinais celulares por meio de ativação proteica no meio extracelular por agonistas do receptor (FONSECA *et al*., 2004 e FANELLI e BENEDETTI, 2005).

Sendo assim, a partir da ligação de endocanabinoides ou canabinóides aos receptores ocorre a regulação dos níveis de Monofosfato cíclico de adenosina (cAMP), de forma a reduzir a concentração plasmática deste, por meio da inibição do adenilil ciclase (AC). Além disso, os receptores endocanabinoides quando ativados também aumentam o nível de proteínas quinase ativadas por mitógeno (MAKP) (WANG; UEDA, 2009 e TANASESCU; CONSTANTINESCU, 2010).

Há dois outros receptores que são ativados pelos canabinóides chamados de receptores de potencial transiente vanilóide do tipo 1 (TRPV1) e o receptor acoplado à proteína G 55 (GPR55, da sigla do inglês G protein-coupled receptor 55), o último sendo estabelecido como um receptor endocanabinoide com sinalização diferente de CB1 e CB2 (KOKONA *et al*., 2016 e LAUCKNER *et al*., 2007).

Os endocanabinoides agem como agonistas dos receptores CB1 e CB2. A Anandamida (AEA), primeiro a ser descrito por Devanne (1992), tem quatro vezes mais afinidade por CB1 do que por CB2, sendo considerada agonista parcial e agonista fraco para estes receptores, respectivamente. Já o 2-araquidonilglicerol (2-AG) é considerado agonista total de ambos os receptores, mas com mais afinidade a CB1 que CB2 (WANG; UEDA, 2009 e SVÍŽENSKÁ *et al*., 2008).

Os ligantes endógenos do SEC são derivados do ácido aracdônico (AA) conjugados com glicerol ou com etanolamina. A AEA é biossintetizada a partir de fosfolipídios da membrana pela via de “transacilação-fosfodiesterase” em que a primeira reação desta via é a N-acetilação da fosfatildietanolamina pela enzima N-acetiltransferase (NAT) e esta reação é desencadeada pelo aumento da concentração de íons de cálcio. O segundo passo da via é uma hidrólise do produto resultante da primeira reação pela enzima N-acil fosfatidiletanolamina fosfolipase D-específica (NAPE-PLD), resultando então na AEA (FONSECA *et al*, 2004 e WANG; UEDA, 2009).

Apesar de serem ambos derivados do AA, a biossintetização de AEA e de 2-AG não seguem a mesma via. O 2-AG é formado a partir de hidrólises de fosfolipídios de inositol contendo ácido aracdôncico pelas enzimas fosfolipase c (PLC) e diacilglicerol lipase (DAGL), respectivamente (WANG; UEDA, 2009).

Os endocanabinoides, diferente de outros neurotransmissores e neuropeptídeos, não são armazenados em vesículas, mas sim produzidos sob demanda ou necessidade por enzimas intracelulares seguido de ação nos receptores e inativação por enzimas por meio de hidrólise. (WANG; UEDA, 2009). A degradação do AEA é feita rapidamente pela enzima amida hidrolase de ácidos graxos (FAAH,do inglês fatty acid amide hydrolase) por esta ser extremamente instável, e a degradação do 2-AG é feita pela enzima monoacilglicerol lipase (MAGL) (SVÍŽENSKÁ *et al*., 2008 e DE PRETROCELIS *et al*, 2009).

Além dos endocanabinoides existem substâncias exógenas que atuam nos receptores CB1 e CB2, podendo derivar da *Cannabis sativa* ou serem sintéticas. Os mais conhecidos e discutidos são o Δ^9-tetrahidrocanabinol (THC), um composto psicoativo, e o canabidiol (CBD), que não possui propriedades psicoativas (CHYE *et al*., 2021 e LU; MACKIE, 2021).

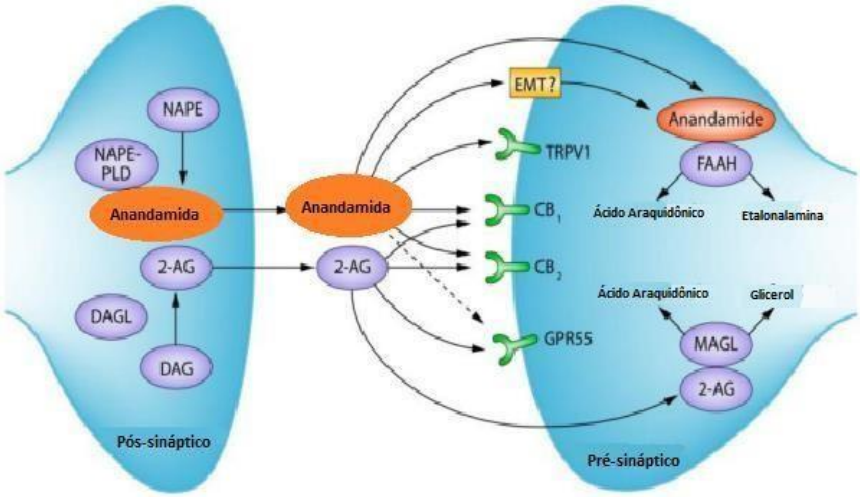

Figura 1: Mecanismos de síntese e degradação dos endocanabinóides 2-AG e AEA. Na imagem também são ilustados receptores aos quais os compostos atuam. Fonte: adaptada e traduzida para o português de Zhou *et al*., 2019

Os receptores CB1 são encontrados em alta a moderada densidade na maioria das regiões do SNC, como o córtex cerebral, o gânglio de base, substância cinzenta periaquedutal, hipotálamo, amígdala e cerebelo. Estes receptores encontram-se também no sistema nervoso simpático, parassimpático, somático e entérico (HASPULA; CLARK, 2020).

Para além do sistema nervoso outras regiões também expressam receptores CB1 em menor quantidade, como, fígado, tecido muscular, adipócitos, sistema vascular, coração, células beta pancreáticas, órgãos reprodutivos e células alveolares (HASPULA; CLARK, 2020).

Já os receptores CB2 são pouco expressados no sistema nervoso em condições fisiológicas normais, havendo suprarregulação destes em células gliais quando em situação neuroinflamatória. Porém, há uma alta expressão deles em órgãos linfóides e células que participam das respostas imunes inatas e adaptativas, como no baço, timo e células mononucleares do sangue periférico (HASPULA; CLARK, 2020).

A figura 2 demonstra de forma resumida a distribuição tecidual dos receptores CB1 e CB2.

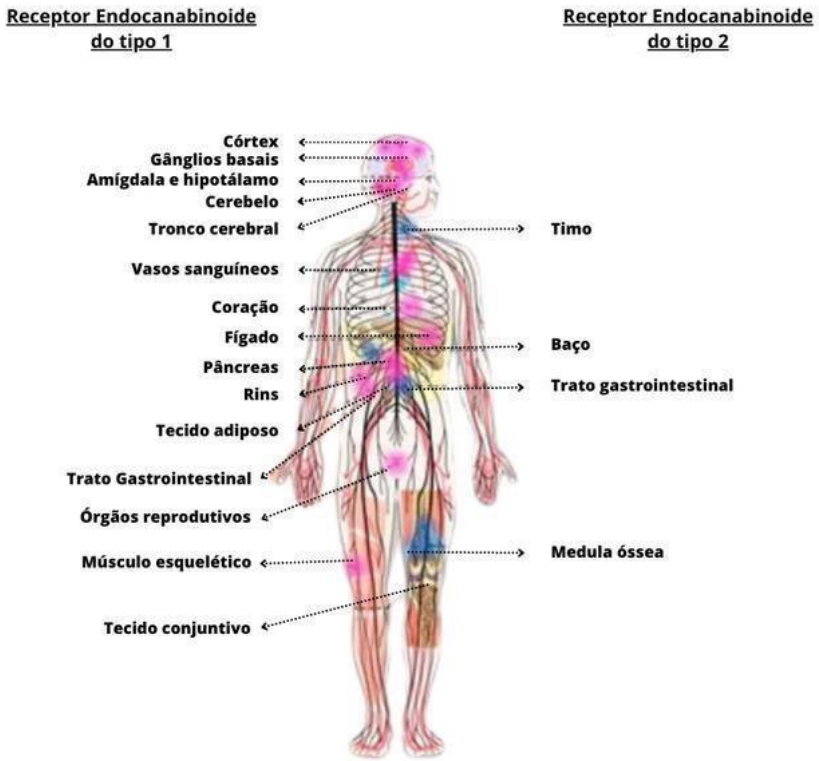

Figura 2: Sob condições fisiológicas normais o receptor CB1 se expressa principalmente no SNC e o CB2 se expressa em tecidos associados ao sistema imunitário. Fonte: Adaptado para o português de HASPULA *et al*., 2020.

2.2. Atuação do Sistema Endocanabinoide no Sistema Imunitário

Embora o receptor CB2 seja mais associado com o sistema imunitário e as células comprometidas nele, um estudo feito por GALIÈGUE *et al*. (1995) que analisou o padrão de distribuição de CB1 e CB2 em células imunitárias purificadas, pôde-se encontrar também receptores CB1 em linfócitos B, células *natural killers* (NK), neutrófilos polimorfonucleares, linfócitos T e monócitos. Este estudo também constatou que CB2 se expressava em quantidades maiores nos linfócitos B, seguido das células NK, monócitos, células polimorfonucleares, linfócitos T8 e T4, respectivamente.

Em relação às células B, RAHAMAN e GANGULY (2021) resumiram que a relação entre elas e o sistema endocanabinoide é o papel duplo do endocanabinoide 2-AG, que atua tanto na atração de células T virgens e células T de Zona Marginal por meio de quimiotaxia, quanto na inibição da função das mesmas que foram atraídas.

Nas células NK o efeito que se observa é o aumento da migração destas células induzidas por 2-AG e com envolvimento do receptor CB2. Esta migração é benéfica no mecanismo de defesa contra vírus infecciosos e cânceres (KISHIMOTO *et al*, 2005).

Para os monócitos, a AEA está envolvida na regulação da função de forma dose e tempo dependente. (RAHAMAN; GANGULY, 2021). Em estudo realizado para avaliar o efeito de AEA na produção de citocinas por células sanguíneas humanas mononucleares periféricas estimuladas foi demonstrado que em concentrações nanomolares de anandamida, Interleucina-6 (IL-6) e Interleucina-8 (IL-8) têm suas concentrações diminuídas e que em concentrações maiores inibe a produção de interleucina 4 (IL-4), fator de necrose tumoral alfa (TNF-α, do inglês Tumor necrosis factor) e interferon-gama (IFN-|)(BERDYSHEV *et al*., 1997).

Além disso, a partir do aumento de doses de 2-AG através do receptor CB1, monócitos humanos primários demonstram aumento da produção de óxido nítrico. O tratamento com 2-AG também os torna imóveis, reduzindo a produção de citocinas (STEFANO *et al*., 2000).

As células polimorfonucleares associam-se ao sistema endocanabinoide por meio de efeitos estimulatórios por 2-AG e AEA, enquanto também, em grande parte, suprimem a migração destas células (RAHAMAN; GANGULY, 2021).

Nas células T, Rahaman e Ganguly (2021) descrevem que a AEA tem efeitos inibitórios na proliferação dessas, além de fazerem a supressão na liberação de citocinas por linfócitos T CD4+ e T CD8+, e inibição de respostas pró-inflamatórias das células T. Já 2-AG diminui a proliferação destas células induzidas por CD3/CD28, causando uma diminuição na expressão de interleucina-2 (IL-2) e IFN-|, independente dos receptores endocanabinoides.

2.3. Fisiologia da COVID-19

Do grupo de vírus de RNA de fita simples envelopados, o Betacoronavirus (β-CoVs) SARS-CoV-2 é responsável por uma pandemia com início declarado em março de 2020. A disseminação do vírus se iniciou em Wuhan na China em dezembro de 2019, esta cidade foi depois considerada o epicentro da circulação da doença COVID-19 (GUSEV et al., 2022 e KHANMOHAMMADI; REZAEI, 2021). As formas de transmissão da doença incluem o contato com gotículas, aerossóis, fômites, fecal-

oral, urina, saliva e de animais para humanos. (Organização Mundial da Saúde, 2020)

A sintomatologia típica da doença COVID-19, como descrita por Shoaib et al. (2021), inclui fadiga, febre, tosse seca, mal-estar, dor na garganta, perda de olfato e/ou paladar, e em alguns casos, falta de ar, diarréia e sinais característicos de pneumonia viral.

A glicoproteína de spike S do SARS-CoV-2 é responsável por fazer fusão membranar e penetração viral. Essa proteína faz ligação principalmente com o receptor membranar da enzima conversora de angiotensina 2 (ACE2), expressada em células epiteliais, macrófagos, plaquetas, células endoteliais, células do músculo estriado e muitas outras (GUSEV et al., 2022). A elevada expressão de ACE 2 nas células epiteliais do trato respiratório seria determinante para o desenvolvimento da infecção do trato respiratório inferior (WÖLFEL et al., 2020).

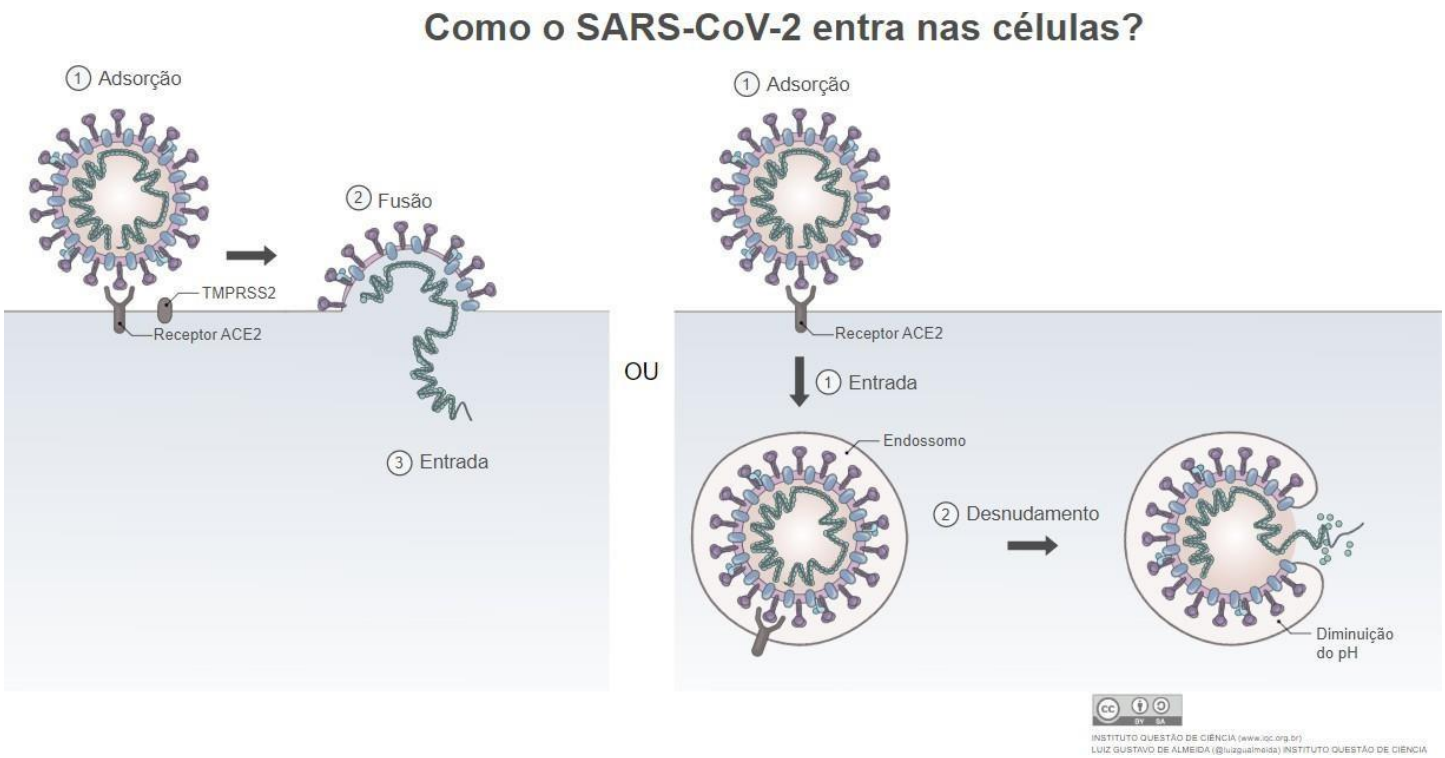

Figura 3: Mecanismo de entrada e replicação do SARS-CoV-2 nas células expressantes de ECA2.
Fonte: Hoffman et al., 2020 adaptado por Luis G Almeida.

Para entender a patogênese da COVID-19 é importante entender os mecanismos de defesa do organismo desencadeados por infecções virais. Sendo assim, Okamoto et al. (2017) descreve que a partir do reconhecimento do RNA viral

pelos Receptores de Reconhecimento de Padrões, como receptores Toll-like (TLR, do inglês toll-like receptors), ocorre a ativação da resposta imune inata.

Entretanto, os betacoronavírus desenvolveram diversos mecanismos a fim de evadir esta resposta, como a produção de antagonistas Interferon-I (INF-I). Os Interferons I e II são transcritos após a ativação dos TLR e desencadeiam a transcrição de genes anti-virais (Harrison et al., 2020).

Outro mecanismo importante para o combate à infecções virais é a resposta imune adaptativa, que ocorre com a ativação de linfócitos TCD8, células associadas com a destruição de células infectadas por vírus, e de linfócitos B responsáveis pela produção de anticorpos que atacam antígenos (ZHONG et al, 2020).

De acordo com estudo feito por Varchetta et al. (2021), quando feita comparação da concentração de células T e Natural Killers entre pacientes com COVID-19 e pacientes saudáveis, os infectados demonstraram perfil imunológico marcado por aumento da expressão de células NK e diminuição da expressão de células T.

Outro fator a ser considerado na infecção por SARS-CoV-2 é a robusta e persistente resposta viral, que acaba por causar grande produção de citocinas pró-inflamatórias e danos aos tecidos do hospedeiro, conhecida como "tempestade de citocinas" associada a progressão da doença e morte (ZHONG et al, 2020).

3. Justificativa

De acordo com o Painel COVID-19, um veículo de informação criado pelo Ministério da Saúde que divulga dados sobre a situação epidemiológica da COVID-19 advindos da Secretaria de Vigilância em Saúde, até o dia 13 de janeiro de 2023, a incidência de casos de infecção pelo SARS-CoV-2 era de 17,62% e a taxa de mortalidade de 33,1%, aproximadamente. Sendo assim, torna-se necessário entender os mecanismos pelos quais o vírus atua na enfermidade. Devido ao amplo espectro de atuação do sistema endocanabinoide nas funções fisiológicas, inclusive em sítios em comum com a doença, é de grande relevância entender se ele atua na COVID-19.

4. Objetivos

4.1. Geral

Avaliar a literatura existente que aborda o sistema endocanabinoide e a COVID-19, a fim de explorar a relação entre os dois e a pertinência dos componentes do sistema endocanabinoide e os canabinoides exógenos para o curso da infecção por SARS-CoV-2 tanto na fase aguda quanto nas sequelas da chamada COVID-longa.

4.2. Específicos

- Revisar a literatura atual sobre o sistema endocanabinoide e sua relação com a COVID-19;
- Analisar estudos que investigam a influência dos componentes do sistema endocanabinoide na evolução da infecção por SARS-CoV-2;
- Identificar possíveis mecanismos pelos quais os canabinoides exógenos podem influenciar o curso da COVID-19;
- Investigar a relação entre o sistema endocanabinoide e as sequelas da COVID-longa;
- Avaliar a pertinência de utilizar componentes do sistema endocanabinoide e canabinoides exógenos como tratamento para a COVID-19.

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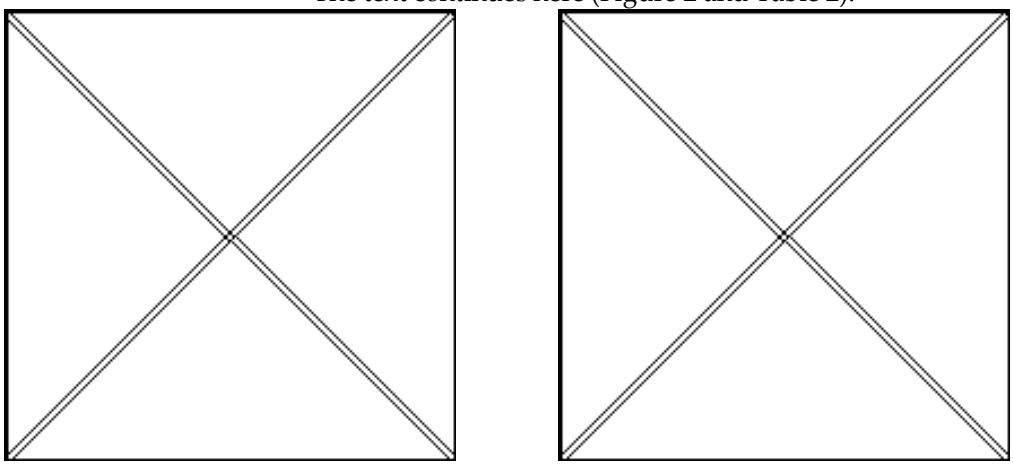

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7. Artigo

Review

The Association Between the Endocannabinoid System and SARS-CoV-2: A Scoping Review

Mariana Martins Guida ; Margô Gomes de Oliveira Karnikowski; Vivian da Silva Santos

Universidade de Brasília

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Abstract: The endocannabinoid system, composed of CB1 and CB2 receptors and its endogenous agonists AEA and 2-AG, plays a role in various biological processes such as regulating immune function, behavior, and metabolism. The endocannabinoid system has been linked to the modulation of immune cell functions, and its anti-inflammatory properties have been studied in relation to diseases such as diabetes, cardiovascular disorders, cancer, and autoimmune diseases. There may be a correlation between the endocannabinoid system and the SARS-CoV-2 virus and understanding this connection can aid in understanding the mechanisms of the virus, inflammation, and treatment. In summary, the present study is a scoping review that aims to provide an overview of the existing knowledge on the topic of the endocannabinoid system and its relation to coronavirus disease (COVID-19). The study was conducted using the terms "Endocannabinoid System", "Endocannabinoids", "Coronavirus" and "COVID" and the Boolean operators "AND" and "OR". The search results were filtered using inclusion and exclusion criteria, and the eligible articles were critically analyzed to synthesize the findings and identify gaps in the literature. The study was completed on January 7th, 2023, and the results were grouped into different moments of COVID-19 disease. The selected 13 articles analyzed the role of endogenous and exogenous substances in mitigating the impact of SARS-CoV-2, the virus that causes COVID-19. The articles were divided into three categories: prior to infection, during infection, and "Long-Covid," which refers to symptoms that persist even after the end of the disease. Three papers were included in the first group, seven in the second, and three in the last.; Considering the discoveries made in this work it is possible to infer that COVID-19 is directly affected by the endocannabinoid system's action, determining factors like disease infectivity, inflammation, and recovery. COVID-19 pathophysiology is also a mean which can be used to understand better the endocannabinoidome and its interaction with the traditional and well-known endocannabinoid system. With, further studies are needed to better understand this system's relation with disease.

Keywords: COVID-19; Endocannabinoid system; Endocannabinoidome; Long COVID

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1. Introduction

Advances in medicine have allowed for a new emphasis on the endocannabinoid system and its importance in the body's biological processes. This system is composed of: i) cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) receptors; ii) its known endogenous agonists anandamide (AEA) and 2-arachidonylglycerol (2-AG), as well as iii) enzymes responsible for the synthesis and degradation of endocannabinoids [1].

CB1 and CB2 receptors are located in the central nervous system (CNS), peripheral nervous system (PNS), organs, glands and immune cells, exerting neurological, metabolic, behavioral and immunological functions [1]. They are expressed in different proportions throughout the body, with CB1 mostly found in the nervous system, while CB2 can be found mostly, but not exclusively, peripherally associated with the immune system (mainly Lymphocyte B cells and Macrophages), and its activation is related to anti-inflammatory properties [2,3]

In addition to the CB2 receptor being strongly associated with the immune system, the endocannabinoids AEA and 2-AG are lipid compounds derived from arachidonic acid similar to the prostaglandins involved in inflammation processes. [4]. According to Klein *et al* another possible relationship between the endocannabinoid system and the immune system is the modulation of immune cell functions through signals mediated by CB1 and CB2 [5].

The mechanisms behind the immunomodulation performed by the endocannabinoid system and its anti-inflammatory properties are not yet fully elucidated, but there is already a description in the literature of its possible role in a range of diseases, such as diabetes, disorders of the cardiovascular system, cancer, and autoimmune diseases [6]

According to Tanasescu and Constantinescu [3], endocannabinoid receptors are involved in the negative feedback process of cyclic adenosine monophosphate (cAMP), which, in turn, is modulated by the enzyme Adenylate Cyclase (AC). The activity of these compounds is associated with the activation of lymphocytes and the transcription of cytokines by macrophages [3].

It is important to mention that the mediation caused by the endocannabinoid system occurs in a way that there may be a suppression of cytokines that potentiate inflammation [3]. This is of great relevance when associated with infection by SARS-CoV-2, the etiological agent of COVID-19, as the most severe cases have been associated with the so-called “cytokine storm”[7].

Considering the relationship between the endocannabinoid system and the immune system established in the current scientific literature, it is possible that there is a correlation between this system and infection by the SARS-CoV-2 virus. In this perspective, the elucidation of this connection can help in understanding the mechanisms of infection, inflammation, and cure of the disease.

2. Materials and Methods

The present study is a scoping review of the literature, which, through the definition of a given topic of discussion, establishment of search criteria such as database, descriptors and inclusion and exclusion criteria, extraction of information from the resulting articles, and critical analysis of the information, a discussion and synthesis of the results are made, giving an overview of the existing knowledge of the topic and identifying gaps in the literature.

It was carried out through a bibliographic search on the Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed) and Web of Science (Thompson Reuters) platforms, using the terms "Endocannabinoid System", "Endocannabinoids", "Coronavirus" and "COVID" and the Boolean operators "AND" and "OR".

Therefore, at first, a search was carried out in each of the databases, extracting information such as: Title, publication date, authors, DOI and abstract, this stage having been completed on 01/07/2023. A table with all the cited information was built with the results from the two database platforms.

Among the inclusion criteria were: original articles; publication between the years 2020 and 2023; articles in English and articles that adhere to the proposed theme.

Then, the titles and abstracts were read to exclude articles that were not in accordance with the inclusion criteria. Those that continued in analysis after this exclusion underwent a process of full-text screening to then determine eligibility to participate in the review.

3. Results

From the PubMed database 42 results were obtained from the search, and 38 were obtained from the Web of Science database, adding up to a total of 80 articles. These results were analyzed for duplicates, leading up to a removal of 30 articles. A summary of the screening can be found in figure x.

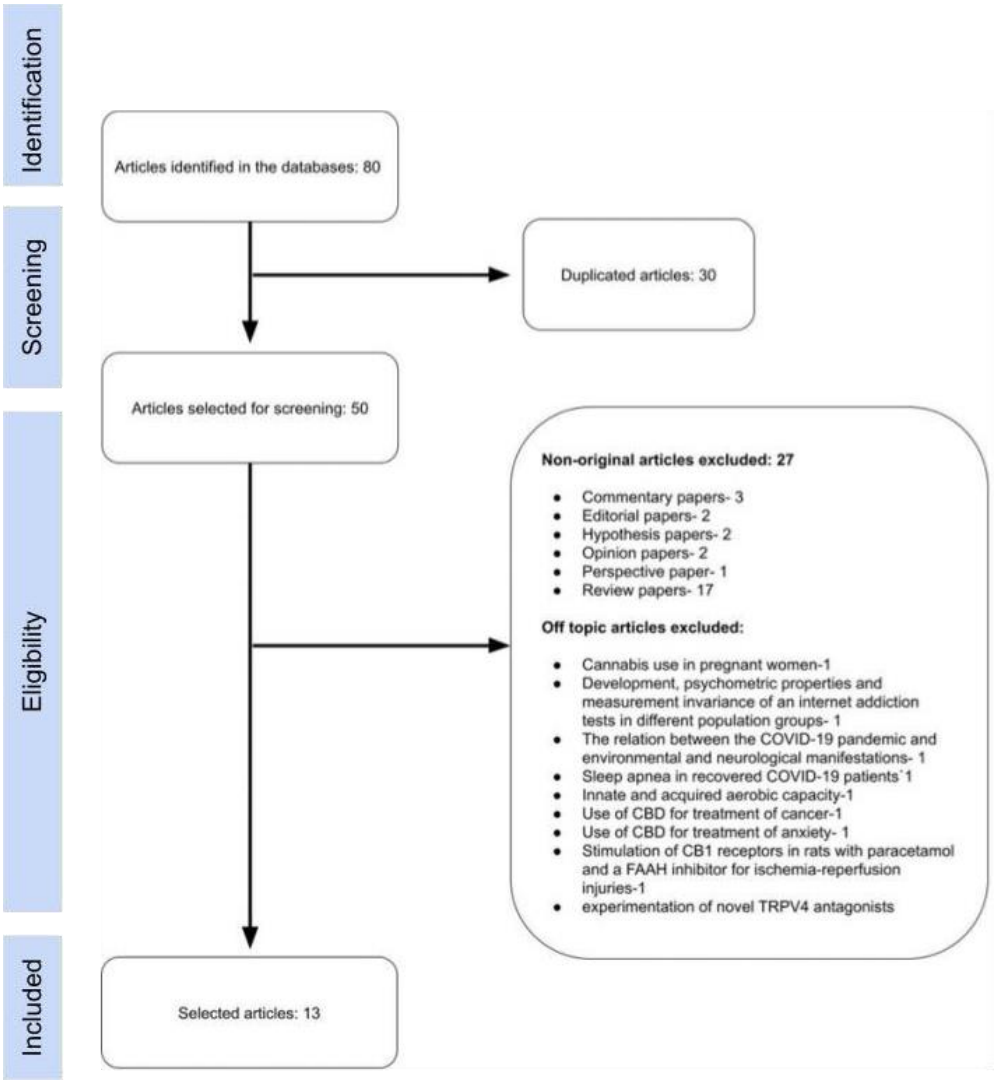

Figure 1. Flow chart of article selection process

The 13 articles selected to be analyzed in the final product were divided into three different categories, encompassing the moment prior to infection, the moment during infection and the so-called "Long-Covid", a series of symptoms that persist even after the end of the disease

3.1. Prior to Infection

Articles exploring the moment prior to infection suggest utilizing both endogenous and exogenous substances to mitigate viral infection and infectivity.

In a study by Fonnesu *et al*. [8] conducted in 2022, the endogenous substance Palmitoylethanolamide (PEA) was administered to various cell cultures to assess its impact on the binding between SARS-CoV-2's spike

(S) protein and ACE 2 cell receptors, as well as on viral replication [8].The results showed that PEA effectively bound to the S proteins, reducing their expression and hence, their binding to ACE 2, ultimately decreasing viral entry into the cells. Additionally, the study highlighted PEA's capability to decrease the content of fatty acid liquid droplets, a crucial component for viral replication [8].

Santos *et al*. conducted a study in 2022 on various combinations of CBD and terpenes as a potential solution to mitigate SARS-CoV-2 infectivity. Six formulations were evaluated in vitro on various cell cultures to assess their impact on factors involved in SARS-CoV-2 infectivity such as viral reduction, expression of ACE2, transmembrane protease serine (TMPRSS2), RdRp and Spike proteins [9]. The results showed that some of the formulations were capable of reducing infectivity in specific cells by up to 99%, while others were found to be cytotoxic to cells. Additionally, the study found that the addition of CBD to the terpene formulations was beneficial, as it had an additive effect and required decreased concentrations of terpene to produce the same effect [9].

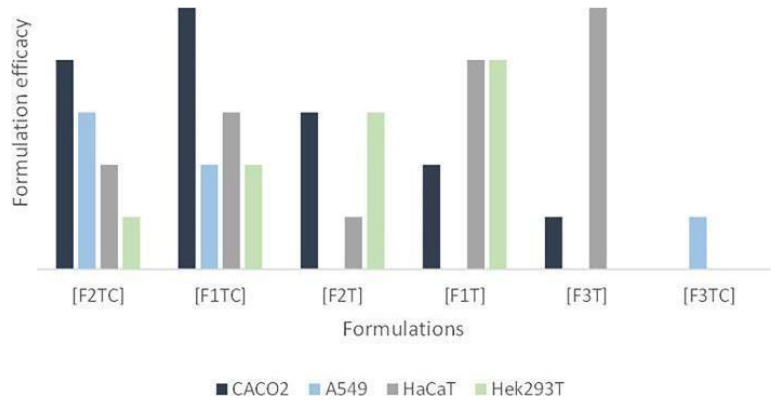

Figure 2: Efficacy on reduction of viral replication of formulations tested by Santos *et al*. the terpene and cannabidiol formulations F2TC and F1TC showed additive effects in comparison to the terpene only formulations F2T and F1T in CACO2, A549 and HaCaT cells, and CACO2 and A549 cells, respectively. F3T and F3TC was cytotoxic in most cell lines [9].

The article by Rastegar *et al*. published in 2021 explored the role of polymorphisms in the cannabinoid receptor CB2 in COVID-19 by using molecular docking to study the interaction between the CB2-Q63R polymorphism and the G protein. The results showed that the CB2-Q63R polymorphism does not bind to the G protein in the correct position, suggesting that it may be a factor contributing to the severity of COVID-19 infections [10].

Based on the studies mentioned in the article, it appears that both endocannabinoids and exogenous cannabinoid substances have been teste for a potential impact on mitigating SARS-CoV-2 infectivity. Additionally, factors preceding infection connected to the endocannabinoid system were studied for whether they alter disease severity or not.

3.2. During infection

		Endocannabinoid System												Immune System				Effects/Findings
Article	Vehicle/Subject	CB1	CB2	CB2Q63R	AEA	2AG	FAAH	LG	OG	PEA	OEA	Meth-AEA	CBD	TNFα	IL-10	IL6	IFNγ	PPAR-α	
Aghamadi et al.,	Peripheral blood monocyte cells of COVID-19 patients.	↑	↑																Elevation of theses composts were associated with severe and moderate COVID-19 patients.
Aswad et al., 2022	Mouse Macrophages												↑			↓			In an overview, CBD administration reduced acute inflammation
	Human Neutrophils												↑	↓		↓			
	Human Peripheral Blood Monocite Cells												↑	↓		↓	↓		
	Human CD4+ T cells												↑	↓		↓	↓		
	Human CD3+, CD4+ T and CD8+ cells												↑						
	Peritoneum of LPStreaded mice												↑	↓					
	Blood of LPStreaded mice												↑	↓	↑				
	Lung fluid of LPStreated mice												↑	↓	↑				
	Leukocyte marker CD45+ of LPStreated mice												↑						
	Lung tissue of LPStreated mice												↑			↓			
Flannery et al., 2021	poly I:C induced activation of TLR3 in the hypothalamus											↑							Did not alter TLR3 induced inflammatory gene
										↑									
											↑								Atennuated TLR3 induced inflammatory gene expression
	poly I:C induced activation of TLR3 in the										↑								Did not alter TLR3 induced inflammatory gene
										↑									
	poly I:C induced activation of TLR3 in the hypothalamus with PPAR-α antagonism										↑							↓	No atennuation of inflammatory genes
Karu et al., 2022	COVID-19 plasma Oxylipins and their precursors					↑		↑	↑										Elevation associated with patients in the intensive care unit
Palmos et al., 2022	Blood protein levels						↑												Elevation associated with risk of hospitalization
Sultan et al., 2021	SEBmediated inflammation in mice lungs				↑														All parameters of lung function mesured improved
					↑														SEBinduced increase of IL6 was lowered after treatment
	Histopathological analysis of lungs after SEBmediated inflammation				↑														Decrease of infiltration of inflammatory cells
					↑														Decrease of leakage in the lungs
	Histopathological analysis of the colon after SEBmediated inflammation				↑														Decrease of infiltration of inflammatory cells
					↑														Decrease of leakage in the colon
	Mesenteric lymph nodes				↑														T cell population was decreased
	Cells expressed in the lungs																		Induces T regulatory cells
					↑														Induces AMP expression
																			Induces tight junction proteins
	Microbial profile in lungs and gut				↑														Induces beneficial bacteria
					↓														Induces pathological bacteria
					↑														Increase of bacteria that produce butyrate
Zarcovik et al., 2022	Phospholipid plasma levels of COVID-19 patients				↑	↑													Recovered COVID-19 patients
										↑	↑								Deceased COVID19 patients

Figure 3: Summary of the results obtained in articles regarding the course of COVID-19 infection.

The use of CDB was also evaluated as an alternative treatment to COVID-19 by Aswad et al. in 2022, but this time, focusing on its anti-

inflammatory action. The authors hypothesized that CBD extracts could help to regulate the cytokine storm, a hallmark of the disease, which is characterized by hyperinflammation [11]. To test their theory, the researchers selected a specific CBD extract, CBD-X, composed of 35% CBD and 0.3% THC, from a pool of 6 different formulations. CBD-X was chosen based on its ability to reduce the pro-inflammatory cytokine IL-6 by 50% in mouse macrophages [11]. This extract was found by the authors to additionally decrease secretion of other inflammatory cytokines, like TNF-α and IFN-γ in vivo and in vitro. An in vivo model treated with CDB-X also increased production of the anti-inflammatory cytokine IL-10 [11]. Therefore, the authors conclude that this CBD extract can be used in conditions such as COVID-19, where cytokine secretion and inflammation responses are dysregulated [11].

Flannery et al. studied the role of inflammation in COVID-19 with a focus on Toll-Like Receptor 3 (TLR3) activation in 2021. The authors believed that since other viral antigens activate TLR3, this mechanism may also play a role in COVID-19 [12]. To test this, the authors focused on endocannabinoid-like substances N-oleoylethanolamide (OEA) and N-palmitoylethanolamide (PEA) and an endocannabinoid analogue of anandamide (METH-AEA) as they are believed to have anti-inflammatory properties [12]. The study used poly I:C to induce TLR3-induced hyperthermia and inflammatory gene expression, and OEA, PEA and Meth-AEA were used to treat these conditions. The results showed that OEA was able to reduce inflammatory gene expression in the hypothalamus, but neither Meth-AEA nor PEA were able to reduce it [12]. In the spleen, however, none of the N-acylethanolamines were effective in reducing the expression of inflammatory genes. Further experimentation with a peroxisome proliferator-activated receptor (PPARα) antagonist and OEA revealed that the reduction of inflammatory gene expression seen in the hypothalamus was partially mediated by PPARα, a mean through which the author says that OEA an PEA modulate anti-inflammatory and neuroprotective effects [12].

The study by Aghamadi et al. conducted in 2022 analyzed the expression levels of CB1 and CB2 receptors in COVID-19 patients with and without diabetes. 80 participants were divided into eight groups based on the severity of their COVID-19 symptoms and their diabetic status [13]. Results showed that severe and moderate COVID-19 patients had higher expression levels of CB1 and CB2 compared to healthy individuals, and diabetic patients also had higher expression levels of the receptors compared to control groups of healthy individuals with and without diabetes [13]. The author considered that these findings suggest a potential role of the endocannabinoid system in the severity of COVID-19 and its interaction with diabetes [13].

To further asses the factors that come into play in disease disinvolvement and severity and possible therapeutic targets, Karu et al. conducted a study in 2022 which collected plasma from COVID-19 patients to measure many variables, including acylglycerol (AG), linoleyl glycerol (LG), oleoyl-glycerol (OG) and cytokines involved in COVID-19 disease progression [13]. The authors found that patients in the intensive care unit (ICU) had in common a dramatic increase in AG, LG and OG and were correlated with hyper-inflammation markers [13]. They suggest that the diverse effects of COVID-19 could be a consequence of the differential metabolism of phospholipids and lipid peroxidation in the plasma of patients. They believe that these differences in metabolism

could contribute to the varying severity of COVID-19 symptoms and outcomes seen in different individuals [13].

Palmos et al. conducted a study in 2022 to identify blood proteins associated with COVID-19 disease severity using the mendelian randomization method. They found that fatty acid amide hydrolase 2 (FAAH2), an enzyme in the endocannabinoid system involved in the hydrolyzation of endocannabinoids like AEA and 2-AG, showed the strongest correlation with an increased risk of hospitalization among COVID-19 patients [14].

Sultan et al. explored the potential of AEA to alleviate acute respiratory distress syndrome (ARDS), a severe complication of COVID-19 in 2021. They tested this in mice by first inducing ARDS with Staphylococcal enterotoxin B (SEB) and then administering AEA or a control. The results showed that AEA treatment significantly reduced lung inflammation, IL-6 secretion, and infiltration of inflammatory cells in the lungs and colon [15]. Additionally, it increased the number of regulatory T cells, upregulated the secretion of antimicrobial peptides by lung epithelial cells, and increased tight junction proteins and secretory leukocyte peptidase inhibitor [15]. The study also found that AEA induced the growth of beneficial gut bacteria that produce butyrate, which has been shown to alleviate ARDS, while the control group saw the growth of pathological bacteria that could lead to secondary infections [15].

Much like the study of Karu et al., Žarković et al. evaluated the role of lipid metabolism in COVID-19 in the same year. Blood samples from COVID-19 patients and a control group of healthy subjects were analyzed for levels of endocannabinoid and endocannabinoid-like substances (AEA, 2-AG, PEA, and OEA). COVID-19 patients were grouped based on their disease outcome: recovery or death [16]. The results showed that deceased patients had significantly higher levels of PEA and OEA in circulation compared to the other two groups and had the highest concentrations of the inflammatory cytokine IL-6 in their blood samples. On the other hand, recovered patients had higher levels of 2-AG, primarily, compared to the other two groups [16].

These studies suggest that the endocannabinoid system may play a role in the severity of COVID-19 and its associated symptoms and that certain compounds within the endocannabinoid system may have therapeutic potential for treating the disease.

3.3. Long COVID

The studies by Ergul et al., conducted in 2022, and Versace et al., published in 2023, and Raciti et al., conducted in 2022, focus on the lingering effects of COVID-19 on recovered patients. The first study examines patients with issues with their sense of smell and taste, the second had as subjects long COVID patients attending a neurological clinic, and the third study focuses on patients struggling with cognitive difficulties and fatigue and the third [17-19]

Ergul et al. used magnetic resonance imaging to compare the brain volumes of COVID-19 patients with a control group. They also measured the endocannabinoid levels in the peripheral blood of both groups [17]. The results showed that the COVID-19 patients had smaller volumes in

the right angular gyrus and larger volumes in the left ENT region compared to the control group. Furthermore, the endocannabinoid levels in the COVID-19 patients were elevated and negatively correlated with the volumes of the left and right ENT regions [17].

Raciti and co-workers administered daily doses of PEA to 33 patients from a neurological clinic in Italy for three months. Post-COVID-19 Functional Status was measured for each patient before and after treatment [18]. It was concluded by the authors that treatment was beneficial and that most patients had an improvement in post-COVID-19 functional Status [18].

The study by Versace et al. (2023), in turn, investigated the effects of Co-ultramicronized palmitoylethanolamide/luteolin (PEA-LUT) on neurological functions affected by post-COVID-19. The study design was a randomized controlled trial, which is considered the gold standard for evaluating the efficacy of treatments [19]. The authors found that the treatment induced activity of the GABAB-ergic neurotransmitter system, which is involved in the regulation of various physiological processes, including pain, anxiety, and mood [19]. Additionally, the treatment was found to increase cortical plasticity, which refers to the ability of the brain to change and adapt in response to new experiences and information [19].

The studies above have explored the lingering effects of COVID-19 on recovered patients. The studies also suggest that treatments such as PEA and PEA-LUT may be beneficial for post-COVID-19 symptoms.

4. Discussion

4.1. Viral entry and replication of SARS-CoV-2

Various components of the endocannabinoid system and their effects on COVID-19 have been studied within the articles contained in the results of this study. Two articles in specific focus on viral entry and replication of SARS-CoV-2.

ACE-2 is a receptor expressed in almost all human organs, is mainly found in type II alveolar epithelial cells and acts as a functional receptor for SARS-CoV-2. The virus' S protein binds to ACE-2 and a membrane fusion occurs, leading to viral RNA entry into the cell. It is said that TMPRSS2 is also involved in this process by cleaving of ACE-2, leading to viral uptake [20, 21].

In the study by Santos et al. potential anti-viral activity of CDB, a non-psychoactive constituent of the Cannabis plant, which has been said in current literature to potentially have analgesic, anti-inflammatory, anxiolytic, antipsychotic, and anti-convulsant properties, and a combination of terpenes is assessed as a method of decreasing SARS-CoV-2 infectivity and it is found that some of the formulations made were able to reduce infectivity of cells [10, 22].

This is not the first time that CBD has been evaluated for its activity on viruses. An earlier in vitro study done in 2017 used CDB as a potential treatment for viral hepatitis B (HBV) and hepatitis C. The results of this study are of that CBD was able to inhibit HCV, but not HBV. In addition, in HBV trials there was a cytotoxic effect in the cell cultures utilized. The authors also comment on a dose-dependent effect on HCV [23].

This converses with the results obtained by Santos et al. as they also observed cytotoxic effect on cells in specific CDB concentrations and different effects on inhibition in different concentrations [10]. Expression of necessary proteins for SARS-CoV-2 infectivity were also assesses, including ACE-2, TMPRSS2, the virus' S protein and a RNA-dependent RNA polymerase necessary for viral replication and transcription were also measured and different cell lines were awarded with different effects for each formulation [10].

While both studies demonstrate a potential therapeutic use of CBD against viral replication and entry into cells, they also highlight the importance of determining the optimal concentrations and combinations to be used because of the cytotoxic effects observed [10, 23].

Novel anti-viral activity is also assessed in the study by Fonnesu et al regarding the interaction of PEA and the ACE-2 receptor. The experiment conducted by the authors demonstrate the ability of PEA to bind to SARS-CoV-2's S protein, thus inhibiting binding to cells expressing ACE-2 [8]. In accordance with the results obtained in the molecular docking study, in vitro studies demonstrated that SARS-CoV-2 infectivity was reduced when PEA was administered to cell cultures [8]. Another important result from this experiment is due to its mechanism of action related to PPAR-α, a receptor from a family of nuclear receptors that regulates the expression of genes involved in immune reaction and can be modulated by and modulate endocannabinoids [8] [24].

A review of PEA's potential therapeutic applications states that this compost is from the N-acyl-ethanolamine (NAE) fatty acid amide family and is considered an endocannabinoid-like lipid mediator. This endogenous substance, along with OEA, also a NAE, is said to be a part of a larger signaling system called the "Endocannabinoidome" [25-29].

The endocannabinoidome compromises the traditional components of the endocannabinoid system which encompass CB1 and CB2 receptors, the endogenous ligands AEA and 2-AG and their synthesis and degradation enzymes, plus a number of novel cannabinoid receptors such as TRPV1, G protein-coupled receptor 55 (GPR55) and G protein-coupled receptor (GPR119), and NAEs and 2-Acyl-glycerols (2-AcGs) [25-29].

PEA is described to target, among others, PPAR-α and trigger its activation. For that reason, Fonnesu et al also assessed PEA activity on PPAR-α dependent events, specifically the disruption of liquid droplets, said by the authors to fuel SARS-CoV-2 replication. The results confirmed the disruption by decrease of liquid droplets when they were quantified [8, 24]. The authors state that this is the first time that these mechanisms are tested and put into action, so there is no data from previous studies to back up these results [8].

In conclusion, the endocannabinoid system and its components have been studied for their potential effects on COVID-19 and although the results presented are promising, it's necessary to conduct more studies to fully understand the potential of the endocannabinoid system and its components in preventing COVID-19.

4.2. Disease progression: inflammation and the endocannabinoidome

It is proposed that upon viral entry, toll-like receptors, innate immune receptors, recognize patterns of the virus and activate nuclear factor-kB (NF-kB) and Interferon regulatory factor (IRF). This signaling induces

production of pro-inflammatory cytokines such as IL-6, associated with COVID-19 severity, among others [30].

Another pathophysiological mechanism suggested for COVID-19 is the immune response triggered by pathogen-associated molecular patterns, leading to release of damage-associated molecular pattern, which in turn triggers pro-inflammatory cytokine release [21, 31].

Ultimately, SARS-CoV-2 infection leads to an excessively inflammatory state called "cytokine storm", characterized by a deregulated immune system generated through innate and acquired immune response, that can evolve into acute respiratory distress syndrome (ARDS) in severe COVID-19 patients [21, 31].

Some of the articles found in the present review were somehow associated with the characterization and/or resolution of the disease's inflammatory state and how the endocannabinoid system could be associated with disease prognosis. Collectively, these findings indicate that the endocannabinoidome may be a crucial factor to consider in understanding disease progression and recovery in COVID-19 patients.

One study, conducted by Zarcovik et al, provides particularly intriguing insights into the physiological differences between COVID-19 patients who progress to death and those who progress to recovery [16]. The researchers found that despite the fame that OEA and PEA have as anti-inflammatory agents, deceased patients had higher levels of these signaling lipids in their blood before death, associated with and elevation of the pro-inflammatory cytokine IL-6 [16, 25, 26].

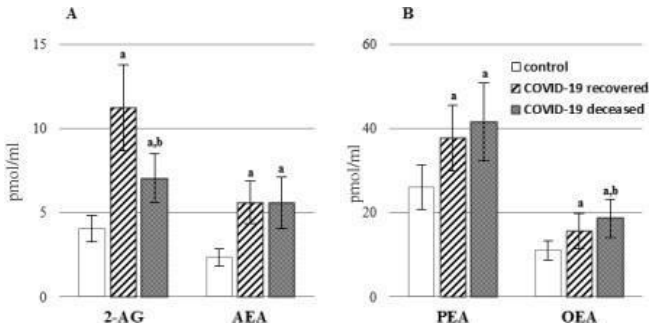

Figure 3: Results from Zarkovic et al. demonstrating increased levels of PEA and OEA in COVID-19 deceased patients in comparison with healthy and recovered patients and increased levels of 2-AG in recovered COVID-19 patients in comparison with healthy and deceased patients [16].

However, in a study by Flannery et al, exogenous administration of OEA caused reduction of TLR3 induced inflammatory genes. This is a contradiction of the obtained data in Zarcokiv et al if considered that endogenous secretion and exogenous administration act in the same manner for every biological signaling composts, but this is not the case in several studies [12, 16].

One study by Potter et al. showed that both had effect on lung resistance, but acted at different fronts, with endogenous NO making more significant effect on tissue resistance and exogenous NO having effect on airway resistance, showing the differential effects of the same compound endogenously and exogenously [31]. Although this study was done in piglets, it is argued that pigs, rather than mice, may be better

animal models for humans because their genome is more alike to humans than to that of the latter [32, 33].

An in vivo experiment on corneal epithelial cells that aimed to study cell migration, adhesion and proliferation with endogenous and exogenous laminin-5 obtained results that agree with the line of thought cited earlier. Exogenous laminin-5 induced mostly cellular adhesion and migration, and as for endogenous laminin-5, cell proliferation was enhanced [34].

This may very well be the case for endocannabinoid-like substances PEA and OEA and could explain why their heightened endogenous levels seem to be associated with COVID-19 inflammation and worse disease prognosis and OEA administration seems to decrease inflammation in a common suggested pathway of SARS-CoV-2 pathophysiology [13, 16].

Be that as it may be, AEA and 2-AG in Zarkovic et al.'s study point towards their possible role as deciding factors in the road towards recovery in COVID-19. It was found that in recovered patients, in comparison with healthy and deceased, 2-AG levels were heightened and AEA levels were increased when compared to healthy volunteers but didn't hold any significant difference to the levels of deceased patients [16].

The same goes for the study by Karu et al, which found that in the plasma of ICU patients endocannabinoid-like substances AG, OG and LG were elevated and associated with inflammatory markers, not promoting inflammation resolution [13]. They go on to hypothesize that this may be due to accelerated catabolism of lipid precursors in various tissues to meet increased demand for free fatty acids and oxylipin synthesis and that the administration of AEA and 2-AG agonists may be of benefit to inflammation regulation, referring once again to these substances' key anti-inflammatory action in COVID-19 [13].

Further evidence in this theory is the study by Palmos et al., that reveals that higher levels of the blood protein FAAH are associated with increased risk in hospitalization [14]. It is proposed in many literatures that FAAH inhibitors can have therapeutic applications. In a study that targeted the regulation of inflammatory pain by this inhibition an attenuation of secretion of pro-inflammatory cytokines IL-1 and TNF-α was seen in an induced inflammatory state in mice [35].

FAAH blood protein is involved in the hydrolyzation of mainly AEA, but also of 2-AG to a lesser extent. Hydrolyzation of these endogenous composts terminates their activity, so it may be that FAAH inhibitors exerts their anti-inflammatory activity by upregulation of these endocannabinoids, explaining the results from Palmos and co-workers [14, 26].

The experiment conducted by Sultan et al corroborates the anti-inflammatory paper of AEA. When administered against ARDS, a COVID-19 triggered condition caused by hyperactivation of the immune system [15]. Lung function parameters ameliorated, and immunosuppressive properties, including attenuation of IL-6 expression were also consequences of AEA administration [15]. Another important consequence is the change in microbial profiles in the lung and the gut. The analyzed group with SEB-mediated ARDS showed presence of pathological bacteria like *Pseudomonas* and *Enterobacteriae*, but not the AEA treated group or naïve group [15].

In an article launched in 2021 by Qu and others it was said that in Shenzhen Third People's Hospital, Pseudomonas aeruginosa is the third

coinfecting bacterium most identified in COVID-19 patients and this bacterial coinfection was associated with critical cases of the disease [37].

Butyrate was also a hallmark of SEB-induced ARDS amelioration, as it was shown to be secreted by AEA induced bacteria and improved disease parameters. Butyrate is shown in other literature to activate a G protein-coupled receptor's (GPCR) signaling, leading to differentiation of T regulatory sells and secretion of anti-inflammatory cytokine IL-10 by T cells [38].

Thus, this study shows the contrary to what was seen in the case of PEA and OEA, that AEA exhibits beneficial effects in both endogenous secretion and exogenous administration, motioning to the need for more in depth research into the mechanism of action of the endocannabinoid-like substances to understand COVID-19 disease severity progression [15, 16].

Disease severity is a topic discussed by Rastegar et al. in 2022 the study about the CB2Q63R polymorphism. It is said by other authors that this variant reduces cannabinoid immune modulation and could determine disease severity of several other conditions [10].

In a study that evaluated disease severity of respiratory disease in children it was found that CB2Q63R was associated with increased risk of hospitalization, much like the results obtained by Rastegar et al in 2022, who concluded that this variant could pose a threat by inducing uncontrolled inflammation, thus affecting disease severity [10, 39].

The study by Aghamadi et al gives an insight into how the endocannabinoid system behaves according to disease severity. Results showed that severe and moderate COVID-19 patients had higher expression levels of CB1 and CB2 compared to healthy individuals [13]. Lakiotaki and colleagues also examined CB1 and CB2 expression in 2015 but had as the object of study malignant and benign thyroid lesions and found that CB1 and CB2 expression was elevated in malignant lesions when compared to benign lesions, especially the CB2 receptor [40].

Authors from the earlier paper point towards a possible prognostic indication through verification of the expression level of these receptors but say that examples of these associations are still contradictory, so it is not possible to affirm what the expression levels say about COVID-19 severity [40].

A form of treatment of COVID-19's hyperinflammation is suggested in the 2022 study by Aswad and group by administration of a CBD extract. This is a treatment proposed for other inflammatory diseases like rheumatoid arthritis and intestinal inflammation [11].

It is shown in other studies that CBD was able to reduce levels of pro-inflammatory cytokines like IL-6 and TNF-α, intimately associated with COVID-19. A result very similar to Aswad et al.'s study, with the addition of CBD also having reduced IL-β and MCP-1 in lung and systemically inflamed mice model and having increased secretion of the anti-inflammatory cytokine IL-10 in a systemically inflamed mouse model[41, 42].

The collection of the articles included in the current review points towards a very present relation between the endocannabinoid system when it comes to the inflammatory state caused by COVID-19 and warrants the need for further research in how the endocannabinoid system and the extended endocannabinoid system, endocannabinoidome, function due to their importance in biological processes associated with inflammation.

4.3. Long COVID

Long COVID can be defined as a series of signs and symptoms that persist after SARS-CoV-2 infection, even after viral clearance has been achieved. Symptoms that may appear include fatigue and dyspnea, being the most common, cardiac abnormalities, cognitive impairment, sleep disturbances, symptoms of posttraumatic stress disorder, muscle pain, concentration problems, hair loss, smell and taste dysfunctions, and headache [43].

To characterize the status of the endocannabinoid system during this state, Ergul *et al* conducted a study to measure endocannabinoid levels in recovered COVID-19 patients with olfactory and gustatory dysfunctions, and these levels were compared with a control group of healthy volunteers [17]. One reason for the relation between the endocannabinoid system and this aspect of long covid is because it is proposed that the olfactory circuitry is affect by physiological changes that alter the olfactory bulb gene regulatory networks [44]. Endocannabinoid system activation is cited as a factor that may contribute to these alterations, seen as reduction of olfactory acuity can be obtained by endocannabinoid mediates reduction of cAMP levels [44].

The research concluded that endocannabinoid levels were elevated in the group of recovered COVID-19 patients with long COVID symptoms. Elevated endocannabinoid levels converse with the theory above, indicating that the elevated expression of these substances deregulate endocannabinoid receptor action, therefore, leading to the dysfunctions aforementioned [17].

A limiting factor to this study is that what specific endocannabinoids were measured and their different concentrations were not disclosed to the readers. This makes it impossible to determine which specific endocannabinoids may be causing this imbalance, warranting for further studies of what aspects of the endocannabinoid system lead to the symptoms of long COVID analyzed [17].

The present review also revealed studies that frame the endocannabinoid system as a medium to treat and cure long covid symptoms. PEA and Ultramicroionized- PEA have been proposed for this purpose [18, 19]. These studies believe that the perpetuation of COVID-19 symptoms that happens in long COVID is due to persistent low intensity inflammation and that PEA administration could help resolve this issue. Indeed, the administration of these composts was awarded with positive results in both studies [18, 19].

In Raciti *et al*., post COVID-19 functional status scores of long COVID patients were improved after treatment. In addition, in Versace *et al*. GABAergic activity and LTP like cortical plasticity was evaluated in patients that described symptoms like fatigue and cognitive dysfunction [17, 18]. GABA activity is associated with cognitive abilities and LTP like cortical plasticity can give an insight into effectiveness of synaptic transmission [18].

The results found in this study enhanced these parameters, hinting at the physiological changes that are induced by PEA administration that could contribute to resolution of long COVID. These results bring forth a possibility of a novel therapeutic approach to this impairment.

5. Conclusions

Considering the discoveries made in this work it is possible to infer that COVID-19 is directly affected by the endocannabinoid system's action, determining factors like disease infectivity, inflammation, and recovery.

COVID-19 pathophysiology is also a mean which can be used to understand better the endocannabinoidome and its interaction with the traditional and well-known endocannabinoid system.

With that being said, further studies are needed to better understand this system's relation with disease.

Conflicts of Interest: The authors declare that this paper proposes a hypothesis.

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