UNIVERSIDADE D
COIMBRA

Fátima Catarina Oliveira Trinco

Relatórios de Estágio e Monografia intitulada "Cannabinoid-based therapies for the treatment of Central Nervous System related disorders", referente à Unidade Curricular "Estágio", sob a orientação da Dra. Maria Helena Costa Neves Correia Amado, Dra. Catarina Seguro Madanêlo e do Professor Doutor Carlos Manuel Freire Cavaleiro, apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas.

Setembro de 2021

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Setembro 2021

Eu, Fátima Catarina Oliveira Trinco, estudante do Mestrado Integrado em Ciências Farmacêuticas, com o n.º 2016230463, declaro assumir toda a responsabilidade pelo conteúdo do Documento Relatórios de Estágio e Monografia intitulada "Cannabinoid-based therapies for the treatment of Central Nervous System related disorders" apresentados à Faculdade de Farmácia da Universidade de Coimbra, no âmbito da unidade de Estágio Curricular.

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Coimbra, 10 de setembro de 2021.

Fátima Catarina Oliveira Trinco

(Fátima Catarina Oliveira Trinco)

Agradecimentos

Aos meus pais, que são o meu pilar e me dão força para enfrentar os desafios que encontro ao longo do meu caminho. Agradeço-vos todo o amor e apoio incondicional. Sem vocês não estaria aqui, não teria conseguido realizar os meus sonhos.

À minha avó, tias, madrinha e primas por todo o apoio e carinho.

À Beatriz, à Elsa, à Inês e à Marta pela paciência e compreensão. Levo comigo todos os momentos que vivemos juntas.

À Vera por ser a melhor afilhada que poderia ter pedido e uma amiga que levarei para a vida.

Aos amigos de longa data por todos os momentos vividos e por todo o apoio.

Ao Professor Doutor Carlos Cavaleiro pela disponibilidade e toda a ajuda prestada na elaboração da presente monografia.

A toda a equipa da Farmácia Luciano & Matos pelos ensinamentos, pelo carinho e principalmente pela amizade.

A toda a equipa do departamento de Assuntos Regulamentares da Bluepharma pelo apoio, confiança, pelo conhecimento que me transmitiram e pela boa disposição.

Obrigada!

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MONOGRAFIA - CANNABINOID-BASED THERAPIES FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM RELATED DISORDERS

RELATÓRIO DE ESTÁGIO FARMÁCIA COMUNITÁRIA

- Farmácia Luciano & Matos -

Sob a orientação da Dra. Maria Helena Amado

Lista de Abreviaturas

APCER – Associação Portuguesa de Certificação

DCI – Denominação comum internacional

FFUC – Faculdade de Farmácia da Universidade de Coimbra

MICF – Mestrado Integrado em Ciências Farmacêuticas

SGQ – Sistema de Gestão de Qualidade

SWOT – *Strengths, Weaknesses, Opportunities, Threats*

1. Introdução

A farmácia comunitária é uma área que marca fortemente o setor farmacêutico, sendo também aquela que possui um maior número de farmacêuticos a exercer. Como indica o nome, esta centra a sua atividade no cidadão da comunidade em que está inserida visando satisfazer as suas necessidades e desejos. O farmacêutico comunitário, enquanto agente de saúde pública, tem uma posição privilegiada de proximidade com o utente podendo contribuir para a promoção de um estilo de vida saudável e participar na gestão da terapêutica fazendo a administração de medicamentos, a determinação de parâmetros e a identificação de pessoas em risco. O farmacêutico pode também contribuir para a deteção precoce de diversas doenças (Ordem dos Farmacêuticos, 2021). Inúmeras vezes os utentes utilizam a farmácia comunitária como o primeiro recurso para solucionar problemas e esclarecer dúvidas relacionadas com o seu estado de saúde.

Dada a importância do farmacêutico comunitário na sociedade, o estágio curricular em farmácia comunitária, englobado no plano de estudos do Mestrado Integrado em Ciências Farmacêuticas (MICF) da Faculdade de Farmácia da Universidade de Coimbra (FFUC), reveste-se de um caráter obrigatório. Sendo a última unidade curricular do MICF, este estágio pretende que os estudantes apliquem o conhecimento adquirido ao longo dos últimos 5 anos em contexto real, dando-lhes a oportunidade de contactarem com o mundo do trabalho antes de terminarem o seu percurso académico e, assim, prepará-los para o futuro.

A minha escolha para a realização deste estágio recaiu sobre a Farmácia Luciano & Matos, onde estagiei durante 4 meses, de janeiro a abril de 2021, sobre a orientação da Diretora Técnica, a Dra. Maria Helena Amado, incidindo o presente relatório sob o mesmo.

2. A Farmácia Luciano & Matos

A farmácia Luciano & Matos conta já com 91 anos de existência. Tendo entrado em funcionamento em 1929 aquando da adjudicação do alvará pelo Ministério da Saúde (Farmácia Luciano & Matos, 2020).

Acumulou as funções de armazém de medicamentos, drogaria e farmácia durante muitos anos, tendo-se dedicado exclusivamente à venda de medicamentos e produtos de saúde em 1995, ano em ocorreu a mudança de proprietário, para a atual proprietária, Dra. Maria Helena Costa Neves Correia Amado (Farmácia Luciano & Matos, 2020).

Localizava-se inicialmente na Rua da Sofia n.º 7-11 onde se manteve até junho de 2009, exceto durante o período de janeiro a fevereiro de 2000, no qual sofreu obras de remodelação

e melhoramento. Em 2009, devido às obras do Metro Mondego, mudou de instalações passando a localizar-se na Praça 8 de maio, n.º 40-42 em Coimbra, onde permanece até aos dias de hoje (Farmácia Luciano & Matos, 2020).

Integrou entre 2009 e 2019 o Grupo Holon (uma marca de farmácias independentes e autónomas, que partilham a mesma imagem e forma de estar). Em 2019, passou a integrar os Grupos BIDS Circle e EZFY, um grupo de compras e serviços, respetivamente, mantendo-se nestes até à atualidade (Farmácia Luciano & Matos, 2020).

3. Análise SWOT

3.1. Pontos Fortes (*Strengths*)

3.1.1. Acolhimento, integração na equipa

No primeiro dia de estágio, os estagiários foram recebidos por um dos membros da equipa da farmácia que nos apresentou as instalações, bem como toda a equipa. A equipa é constituída por 14 elementos: 9 farmacêuticos (nos quais se inclui a diretora técnica, Dra. Maria Helena Amado), 2 técnicos auxiliares de farmácia, um gestor, uma ajudante de *backoffice* e uma funcionária responsável pela limpeza. A Dra. Maria Helena Amado, deu-nos a conhecer a Farmácia Luciano & Matos, falando da sua história até ao presente, bem como da organização e metodologia de trabalho atuais, referindo a metodologia *Kaizen* e o sistema de gestão de qualidade (SGQ), já que a Farmácia Luciano & Matos é certificada pela Associação Portuguesa de Certificação (APCER), de acordo com os requisitos da NP EN ISO 9001:2015.

A Farmácia Luciano & Matos conta já com um longo historial no que respeita à receção de estagiários, tendo demonstrado bastante gosto em nos acolher. Esta equipa mostra uma grande união, cumplicidade e organização, o que se reflete na qualidade dos serviços prestados aos seus utentes e a toda a comunidade. Desde o primeiro momento, todos se mostraram disponíveis para nos ajudarem e esclarecerem qualquer dúvida que surgisse. Os estagiários são considerados membros da equipa da farmácia, participando nas reuniões *Kaizen*, estando sempre a par dos projetos que estão a ser desenvolvidos e dos objetivos que se pretendem alcançar, o que facilitou bastante a nossa integração.

3.1.2. Formação antes de cada fase do plano de estágio e autonomia no desempenho das tarefas

O plano de estágio foi cuidadosamente elaborado, contemplando a passagem dos estagiários pelos vários postos da farmácia permitindo-nos ter contacto com as várias tarefas desenvolvidas diariamente numa farmácia de oficina. Antes da realização de qualquer tarefa é

feita uma introdução teórica detalhada da mesma, sendo-nos também dada a oportunidade de praticar essa mesma tarefa através de simulações ou em contexto real. Este aspeto torna-se de extrema importância, pois até então apenas tomamos contacto com contexto teórico não tendo perceção de como será trabalhar numa farmácia de oficina. Este método de ensino permite-nos ir a pouco e pouco adquirindo novos conhecimentos bem como solidificando aqueles já adquiridos e assim construir as bases necessárias para desenvolver um bom trabalho.

Inicialmente, a realização das tarefas é acompanhada por um membro da equipa mais experiente que assegura que estas estão a ser efetuadas corretamente. Após esta fase inicial é-nos então dada autonomia para realizar as tarefas de forma independente, estando a equipa da farmácia sempre disponível para esclarecer qualquer dúvida que possa surgir. Isto demonstra da parte da farmácia uma grande aposta no trabalho que desenvolve com os seus estagiários e foi para mim uma mais-valia, pois transmitiu-me segurança e permitiu-me ganhar autonomia e confiança no trabalho que desenvolvi.

3.1.3. Metodologia *Kaizen*

A metodologia *Kaizen* surgiu em 1985, no Japão, com a fundação da primeira entidade *Kaizen* Institute Ltd. por Masaaki Ima. O termo *Kaizen* pode dividir-se em duas palavras, "*Kai*" que significa "mudar" e "*Zen*" que significa "para melhor", pelo que, *Kaizen* é sinónimo de melhoria contínua (Kaizen Istitute, 2021).

O *Kaizen* visa a melhoria continua através da criação de valor para o cliente, redução do desperdício, acompanhamento das ações que estão a decorrer, organização de equipas e transparência, sendo atualmente reconhecido como um dos pilares da estratégia competitiva de uma organização (Kaizen Istitute, 2021).

Ao longo do decorrer do meu estágio, a Dra. Maria Helena Amado, bem como toda a equipa da farmácia, procurou transmitir aos estagiários o sentido desta metodologia e os seus princípios. Eram feitas reuniões de aproximadamente 15 minutos regularmente nas quais era analisada a atividade da farmácia e os projetos que estavam a decorrer. Estas reuniões permitiam que toda a equipa se mantivesse atualizada em relação a determinados aspetos, como objetivos a atingir, futuras campanhas, formações, entre outros.

Considero que esta metodologia é indispensável ao bom funcionamento de qualquer organização, pois permite que esta alcance os seus objetivos através do estabelecimento de metas e, fomentando, ao mesmo tempo, o espírito de partilha e interajuda entre colaboradores.

3.1.4. Preparação de um medicamento manipulado

De acordo com o Artigo 1.º do Decreto-Lei n.º 95/2004, um medicamento manipulado é "qualquer fórmula magistral ou preparado oficinal preparado e dispensado sob a responsabilidade de um farmacêutico" (República Portuguesa, 2004).

Com o desenvolvimento da indústria farmacêutica, a preparação de medicamentos manipulados nas farmácias sofreu um decréscimo substancial. No entanto, existem ainda algumas farmácias que fazem esta preparação, sendo uma delas a Farmácia Luciano & Matos. Esta farmácia tem uma grande procura por medicamentos manipulados, tanto de uso humano como veterinário, preparando em média 1000 medicamentos manipulados por mês. Para isso dispõe de dois farmacêuticos, um dos quais a tempo integral, no laboratório de manipulados. Devido ao crescente número de pedidos deste tipo de medicamentos, a farmácia também adquiriu recentemente um *software* que visa facilitar o procedimento de preparação designado Pharma LM.

No decorrer do meu estágio tive a oportunidade de proceder à preparação de 100 ml de uma solução de Minoxidil 5% em Trichosol®, uma solução de uso tópico utilizada no tratamento da alopécia androgénica (Anexo III e Anexo IV). A oportunidade de preparar um medicamento manipulado foi para mim de extrema importância, uma vez que me permitiu reavivar e consolidar conhecimentos previamente adquiridos no decorrer do meu percurso académico, nomeadamente na unidade curricular de Farmácia Galénica.

3.2. Pontos Fracos (*Weaknesses*)

3.2.1. Inexperiência no atendimento

Senti, inicialmente, alguma dificuldade no atendimento ao público devido à minha insegurança quer no relacionamento com o público, quer na utilização do sistema informático.

O atendimento ao público é bastante desafiante requerendo, da parte de quem está a atender, a capacidade de entender as necessidades do utente e de as satisfazer. Embora tivesse já realizado um estágio de verão, não tinha ainda tido a oportunidade de fazer atendimento ao público. Assim sendo, quando comecei a interagir com os utentes, a inexperiência aliada à minha timidez e insegurança tornaram-se entraves ao meu trabalho, nomeadamente em situações de aconselhamento farmacêutico, necessitando por vezes de pedir a ajuda dos colegas. Porém, no decorrer do estágio fui ganhando mais experiência e mais confiança nas minhas capacidades o que me permitiu ser mais autónoma.

O sistema informático utilizado pela Farmácia Luciano & Matos aquando do meu estágio foi o *Sifarma 2000*®. Este *software,* embora bastante útil, pode apresentar-se confuso aos novos utilizadores devido ao vasto número de operações que permite realizar. Requer, por isso, uma grande atenção por parte do operador, nomeadamente em situações mais complexas como o aviamento de receitas manuais e a adição de planos especiais de comparticipação. Contudo, com a experiência tornei-me capaz de realizar estes procedimentos com maior rapidez e eficiência o que me permitiu focar mais a minha atenção nas necessidades do utente.

3.2.2. Dificuldade em associar os nomes comerciais dos medicamentos aos seus princípios ativos

O plano de estudos do MICF é bastante extenso sendo lecionadas várias unidades curriculares nas quais são estudados os princípios ativos dos medicamentos, bem como a sua farmacocinética e farmacodinâmica e utilização em contexto real, através do estudo de casos clínicos. Contudo, este estudo é feito recorrendo à denominação comum internacional (DCI) sendo poucas as vezes em que os princípios ativos são associados aos nomes comerciais dos medicamentos.

Apesar de as receitas serem prescritas de acordo com o sistema DCI, os utentes utilizam frequentemente os nomes comerciais para se referirem aos medicamentos o que, por vezes, me suscitou algumas dúvidas. Inicialmente tinha a necessidade de recorrer à realização de uma pesquisa rápida no sistema de modo a perceber qual o medicamento a que o utente se referia. No entanto, com o passar do tempo, fui-me familiarizando com os nomes comerciais dos medicamentos o que me permitiu responder às necessidades do utente com maior prontidão.

3.3. Oportunidades (*Opportunities*)

3.3.1. Participação em formações

A Farmácia Luciano & Matos é uma empresa bastante dinâmica que procura inovar e melhorar constantemente os seus serviços, e como tal, investe substancialmente na formação dos seus colaboradores, tendo sido dada a oportunidade aos estagiários de também participarem nas mesmas.

Ao longo do meu estágio tive a oportunidade de participar em várias formações, em diversas áreas, organizadas na sua maioria pelo grupo EZFY, nomeadamente "A rota para um intestino feliz", "A "porta aberta" nas infeções respiratórias agudas" e "O papel da farmácia

comunitária na jornada da pessoa com hipertensão", que visam facilitar o aconselhamento ao público.

Tive também a oportunidade de participar numa formação organizada pela Perrigo® na qual foram debatidos alguns dos produtos desta marca, como por exemplo Antigrippine Trieffect®, Vita Cê®, Bronchodual®, entre outros. Estes produtos foram primeiramente apresentados tendo, em seguida, sido descritas algumas das situações nas quais os mesmos poderiam ser aconselhados.

Estas formações foram, para mim, do maior interesse pois permitiram-me não só aprofundar os conhecimentos adquiridos até então como também familiarizar-me com os nomes comerciais dos produtos.

3.4. Ameaças (*Threats*)

3.4.1. Desconfiança perante o estagiário

Embora não sendo uma situação recorrente, alguns utentes demonstravam alguma desconfiança quando o atendimento era feito por um estagiário. Solicitavam por vezes, a opinião de outro colega ou pediam mesmo para serem atendidos por alguém mais experiente, alegando não se sentirem confortáveis com a falta de experiência do estagiário. Tentei veementemente contornar este problema transmitindo a informação de forma clara e assertiva ao utente, respondendo às questões por ele colocadas e demonstrando compreensão para com a sua situação para assim transmitir alguma confiança. Com o decorrer do estágio, este tipo de situação tornou-se cada vez menos recorrente, o que demonstra que este sentimento de falta de confiança por parte dos utentes foi ultrapassado, tendo estes gosto em serem atendidos pelos estagiários.

3.4.2. Medicamentos esgotados

A falta de alguns medicamentos utilizados no tratamento de doenças crónicas é uma realidade das farmácias. Esta falta de medicamentos ocorre quer pela quebra na produção dos mesmos por parte das indústrias farmacêuticas, quer pela quebra na distribuição, devida, por exemplo, à sua exportação para mercados estrangeiros onde o retorno financeiro é maior.

No caso de o medicamento esgotado possuir um genérico que esteja disponível, é possível fazer a substituição do medicamento de marca pelo genérico, explicando ao utente que o medicamento de marca serve de referência à produção do genérico e que este possui a mesma substância ativa na mesma dosagem e está na mesma forma farmacêutica do medicamento de marca. No caso de o medicamento esgotado se encontrar disponível noutra

dose, podemos contactar o médico responsável pela prescrição e sugerir que o utente adquira a dose do medicamento que se encontra disponível, procedendo posteriormente a um ajuste para que corresponda à dose que lhe foi instituída. Contudo, quando o medicamento esgotado não apresenta nenhuma alternativa terapêutica, nem se encontra disponível noutra dose, torna-se necessária a revisão da terapêutica, por parte do médico, de forma a substituir o medicamento esgotado. A troca de laboratório, referida no primeiro caso, ou troca do medicamento, referida no último caso, constituem também uma problemática, especialmente em utentes que trocam a medicação, podendo levar a duplicações da terapêutica.

A falta de medicamentos constitui assim uma ameaça ao funcionamento normal de qualquer farmácia, descredibilizando a posição do farmacêutico perante o utente e afetando possivelmente a confiança que este tem naquele.

4. Conclusão

Após o término do meu estágio em farmácia comunitária, percebo o quão importante este foi no meu percurso académico, contribuindo não só para a minha formação enquanto farmacêutica como também para o meu crescimento pessoal.

As farmácias comunitárias são, sem dúvida, estruturas de saúde extremamente importantes para as populações, sendo, muitas vezes, aquelas que maior proximidade têm dos utentes. Por conseguinte, a farmácia comunitária é, frequentemente, o local preferido pelos utentes para o esclarecimento de dúvidas relativas ao seu estado de saúde e não só. Os farmacêuticos comunitários apresentam-se assim como importantes agentes de saúde pública impactando significativamente a vida de muitos utentes, sendo imprescindível que estejam preparados para enfrentar o mundo do trabalho e todas as adversidades que este venha a apresentar. O estágio curricular em farmácia comunitária é, por isso, da maior importância no percurso académico de qualquer futuro farmacêutico.

Este estágio foi para mim uma oportunidade de contactar com o dia-a-dia de uma farmácia comunitária e perceber as diversas tarefas que são desenvolvidas pelo farmacêutico comunitário, vindo complementar a formação que recebi ao longo dos últimos 5 anos.

A Farmácia Luciano & Matos pauta-se por valores como o espírito de missão, a lealdade, o rigor, a excelência no serviço, a abertura à mudança e a resiliência, valores estes que são essenciais a qualquer farmacêutico comunitário e que são desde cedo transmitidos aos estagiários. Termino assim este estágio certa de que os valores e ensinamentos que me foram passados serão uma mais-valia para o meu futuro enquanto farmacêutica.

5. Casos Clínicos

Caso Clínico 1

Uma jovem de 22 anos dirige-se à farmácia solicitando ajuda pois experiencia desconforto e ardor ao urinar, acompanhados de uma vontade frequente de urinar e sensação de micção incompleta, sintomas estes que se prolongam há algum tempo. Questionei a jovem sobre a presença de mais algum sintoma tendo esta referido sentir uma dor constante ao fundo das costas, do lado direito. Pelos sintomas descritos percebi tratar-se de uma situação de infeção urinária, pelo que questionei a jovem se esta era uma situação recorrente ou se era a primeira vez que tal acontecia, ao que ela me respondeu tratar-se da primeira vez. Questionei ainda a jovem se tomava algum tipo de medicação ou tinha alguma patologia ao que me respondeu que não.

Primeiramente, alertei-a para algumas medidas não farmacológicas que deveria tomar, nomeadamente ingerir muita água, idealmente 1,5L por dia, e alimentos ricos em vitamina C; evitar a utilização de roupa interior sintética e de pensos diários, fazer uma higiene genital adequada e urinar após as relações sexuais.

Aproveitei também a oportunidade para apresentar à utente um suplemento alimentar com extrato de uva-ursina e arando, componentes estes que demonstraram eficácia em ocorrências associadas a infeções do trato urinário inferior. A uva-ursina (*Arctostaphylos uva-ursi L.*), é rica em arbutina, um glicósido da hidroquinona, e taninos que possuem atividade antimicrobiana (Afshar *et al.*, 2018; De Arriba, Naser e Nolte, 2013). O arando (*Vaccinium macrocarpon L.*), embora não apresentando propriedades antimicrobianas possui proantocianidinas do tipo A que inibem a aderência da *Escherichia coli* às células uroepiteliais da bexiga (Lavigne *et al.*, 2008). Esclareci também que este produto embora pudesse ajudar ao tratamento da situação em causa poderia não ser o suficiente para resolver a situação, visto a jovem notar estes sintomas há algum tempo e ter uma dor constante ao fundo das costas (que poderá ser indicativa de que a infeção se terá propagado para os rins). Aconselhei, por isso, que consultasse um médico de forma a que fossem feitos exames complementares de diagnóstico para assim estabelecer qual a patologia e qual o tratamento mais adequado, recorrendo, se necessário, a terapia antibiótica. Apesar de haver uma grande probabilidade de se tratar de uma infeção urinária que se propagou para os rins, não cabe ao farmacêutico fazer diagnósticos nem fornecer terapêutica antibiótica sem prescrição médica.

Por fim referi ainda o benefício das medidas não farmacológicas e suplementos ricos em pré e probióticos, na prevenção da recorrência de infeções urinárias.

Caso Clínico 2

Uma senhora desloca-se à farmácia solicitando um laxante para o marido de 67 anos que estava com prisão de ventre há uma semana e procura uma solução que tenha um efeito rápido. Em conversa com a senhora percebi que esta era uma situação recorrente, pelo que a questionei acerca do estilo de vida do marido, tendo-me dito que ele fazia uma alimentação completa e variada, mas que não praticava exercício físico pois tinha algumas dificuldades em se movimentar. Questionei também a utente sobre o histórico do marido, isto é, se tinha alguma patologia, se se encontrava a tomar algum tipo de medicação, nomeadamente se já tinha alguma vez tomado algum medicamento para a situação que me estava a contar, ao que me respondeu que não.

Embora a esposa tenha referido que o marido praticava uma alimentação saudável, alertei para algumas medidas não farmacológicas que poderiam ser tomadas, nomeadamente a ingestão de bastantes fibras e líquidos e prática de algum tipo de atividade física, mesmo que seja apenas caminhar, uma vez que este tem alguma dificuldade em movimentar-se. Alertei também que seria importante proceder à reeducação do intestino, não inibindo o reflexo de defecação e estabelecendo horários para ir à casa de banho, por norma após o pequeno-almoço, de forma descontraída.

Sugeri a administração de Laevolac® xarope, à base de lactulose, um laxante osmótico que aumenta a fluidez das fezes e leva à sua evacuação. Os laxantes osmóticos têm um tempo de latência de 2 a 3 dias, mas neste caso o utente pretende um alívio imediato pelo que sugeri a administração de uma dose de carga (15 a 30 ml/dia, isto é, 1-3 colheres de sopa diluída em 1/8 a 1/4 de litro de água, café, chá, sumo de fruta ou leite) que leva a que os movimentos intestinais ocorram aproximadamente 2 horas após a toma, originando fezes pastosas ou líquidas. Após a toma desta dose de carga, a lactulose pode ser utlizada durante vários dias, em doses menores (7,5-15 ml/dia, isto é, 1/2 a 1 colher sopa/dia) de forma a regular o transito intestinal, tendo sugerido à esposa do utente que assim procedesse e fosse diminuindo a dose administrada ao longo do tempo, simultaneamente com as medidas de reeducação do intestino anteriormente mencionadas (Ferraz, Lynce, 2008).

Expliquei ainda que a lactulose, em dose adequada, por si só é capaz de eliminar uma obstipação grave não sendo por norma necessário recorrer a laxantes mais agressivos (Ferraz, Lynce, S.A., 2008), mas caso a obstipação persistisse deveria voltar à farmácia para que pudéssemos encontrar outra solução.

Caso Clínico 3

Uma mulher de 30 anos dirige-se à farmácia solicitando ajuda pois sente desconforto e ardor na região íntima que piora durante a relação sexual, referindo também um corrimento branco. Pelos sintomas descritos percebi tratar-se de uma candidíase vulvovaginal, tendo questionado se esta era uma situação recorrente, ao que a utente me respondeu ser a primeira vez que tal acontecera.

Primeiramente aconselhei a utente a tomar algumas medidas não farmacológicas, nomeadamente preferir a utilização de roupa interior de algodão ao invés de fibras sintéticas, evitar o uso de roupa interior apertada bem como de meias calças ou calças justas, praticar uma higiene genital adequada, usar uma toalha, e não um secador de cabelo, por exemplo, para limpar a área genital.

Aconselhei também a aplicação de um creme de clotrimazol, tendo aconselhado Gino-Canesten® em creme pois este traz um aplicador que facilita a aplicação no interior da vagina. Expliquei que a aplicação do creme deve ser feita durante 6 dias consecutivos, à noite, após ir à casa de banho e realizar toda a higiene íntima, preferencialmente na posição de decúbito dorsal, com as pernas ligeiramente fletidas (Bayer Portugal, S.A., 2004).

Bibliografia

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ANEXOS

ANEXO I – RESUMO DAS ESPECIFICAÇÕES DO LABORATÓRIO

glintt

CHECKLIST

AUDITAR ESPECIFICAÇÕES LEGAIS DO LAB

LAB LABORATÓRIO

12	Tamises FP VIII (com fundo e tampa): com a.m. 180µm e 355µm
13	Espátulas metálicas e não metálicas
14	Funis de vidros
15	Papel de filtro
16	Papel indicador do pH universal
17	Matrazes de várias capacidades
18	Pedra para a preparação de pomadas
19	Provetas graduadas de várias capacidades (25, 100, 250 cc)
20	Termómetro (escala mínima até 100ºC)
21	Vidros de relógio

	Sistemas de Conservação:
1	Local de preparação de medicamentos manipulados com sistema de registo de temperatura e humidade (termohigrómetros)
2	Evidência de calibração do termohigrómetro
3	Evidência de controlo semanal do termohigrómetro

	Matérias Primas:
1	Fichas de dados de segurança (FDS)
2	Boletins analíticos das MP armazenadas (validados pelo DT - data, carimbo e rúbrica)
3	Fichas de movimentação de MP (conveniente)
4	Zona segregada para colocação de MP de prazo de validade expirado (obrigatório) ou a expirar (facultativo)
5	Fichas de preparação de manipulados e rotulagem - manutenção durante 3 anos

2/2

glintt

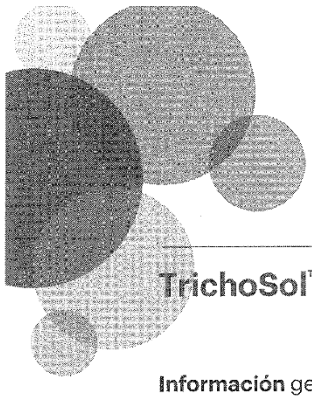
CHECKLIST

AUDITAR ESPECIFICAÇÕES LEGAIS DO LAB

LAB LABORATÓRIO

Nº	DESCRIÇÃO
	LIVROS OBRIGATÓRIOS:
1	Farmacopeia Portuguesa – 9ª Edição, em CD-ROM, e respetivos suplementos (FP 9.0 - Edição Base; FP 9.4 - 4 Primeiros Suplementos; FP 9.5 - 5.º Suplemento; FP 9.6 - 6.º Suplemento; FP 9.7 - 7.º Suplemento; FP 9.8 - 8.º Suplemento)
2	Prontuário Terapêutico - 11.ª edição (2013), em papel ou formato eletrónico, acessível através do site do INFARMED (versões html, pdf e WebMobile)
3	Fichas de Preparação de Manipulados
	IDENTIFICAÇÃO DE DOCUMENTOS:
1	Carimbos: com identificação da farmácia, do diretor técnico, morada da farmácia e contactos
2	Rótulos: com identificação da farmácia, do diretor técnico, morada da farmácia e informações requisitos constantes das boas práticas a observar na preparação de medicamentos manipulados em farmácia de oficina e hospitalar
3	Impressos - papel timbrado e envelopes: com identificação da farmácia, do diretor técnico, morada da farmácia e contactos (conveniente)
	MATERIAL DE LABORATÓRIO OBRIGATÓRIO
1	Sistema de exaustão, câmara de evaporação ou nicho para a eliminação de fumos e gases
2	Local de lavagem de material com água corrente, por cima da bancada de manipulação
3	Balança de precisão sensível ao mg (marcação "CE")
4	Evidência de calibração anual da balança de precisão
5	Evidência de verificação metrológica da balança de precisão
6	Almofarizes de vidro e de porcelana
7	Banho de água termostatizado
8	Alcoómetro
9	Cápsulas de porcelana
10	Pipetas graduadas (sugestão: 1 a 5 cc)
11	Copos de várias capacidades

ANEXO II – FICHA TÉCNICA DO TRICHOSOL™



FICHA TÉCNICA

TrichoSol™

Información general

Solución hidrófila sin alcohol y sin propilenglicol. Con Tecnología TrichoTech™ a base de plantas medicinales .

Identificación

- **Sinonimias:** Base solución hidrófila no irritante
- **Características**
  - Aspecto: Líquido claro a turbio, incoloro a blanquecino, con olor característico
  - pH: 1,5-2,5
  - Densidad relativa: 0,990 - 1,030 g/ml

Propiedades

- Sin parabenos, sin colorantes, sin aceites minerales, sin Lauril sulfato sódico, sin 1,4-dioxano. Sin alcohol y sin propilenglicol.
- Fórmula suave con alta extensibilidad en el cuero cabelludo.
- Compatibilidad única y estabilidad comprobada con APIs (principios activos) e IDCs (ingredientes dermacéuticos) hidrosolubles y liposolubles.

Ventajas

- Vehículo ideal y estable para formulaciones de Minoxidil hasta el 7%.
- Fácil elaboración en dos pasos.
- Para todo tipo de cabello.
- No irritante .
- No causa sequedad capilar.

Aplicaciones

- Alopecia androgenética
- Alopecia areata
- Efluvio anágeno
- Efluvio telógeno
- Cirugía pos-transplante en pacientes con alopecia
- Dermatitis seborreica

Fagron Ibérica SAU
C/ Josep Tapioles, 150
08226 – Terrassa (Barcelona)
Teléfono: +34 937 31 07 22
Fax: +34 937 311 644
www.fagron.es

Fagron personalizing medicine

Ejemplos de principios activos compatibles

- Betametasona dipropionato 0,05%
- Betametasona valerato 0,1%
- Ciclopirox olamina 1 al 1,5%
- Clobetasol propionato 0,05%
- Finasterida 0,1 al 1%
- Fluocinolona acetónido 0,01%
- Latanoprost Fagron 0,005%
- Minoxidil 2 al 7%
- Tretinoína 0,01%

Formulaciones orientativas

Alopecia androgenética	
Minoxidil	2-7%
TrichoSol™ c.s.p.	100 ml

Modus operandi:

1. Pesar el minoxidil reducido previamente a polvo fino.
2. Situar 95 ml de TrichoSol™ en un vaso de precipitados y añadir el minoxidil.
3. Agitar hasta la completa disolución de minoxidil. Para concentraciones elevadas de minoxidil, se puede calentar sin superar los 50ºC durante unos minutos hasta la completa disolución del minoxidil.
4. Filtrar.
5. Añadir trietanolamina sobre la disolución anterior de minoxidil en TrichoSol™ a temperatura ambiente hasta llegar a pH 4-5 (aproximadamente un 3-4%)
6. Enrasar en probeta hasta los 100 ml prescritos con TrichoSol™.
7. Envasar. Etiquetar "Agitar antes de usar".

Minoxidil 5-7 %: El modus operandi es el mismo que el anterior pero en este caso no es necesario regular pH. Evitamos el punto 5.

Caducidad: 3 meses

Posología: 1 ml / 12 horas

Alopecia androgenética	
Finasterida	1%
TrichoSol™ c.s.p.	100 ml

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Modus operandi:

1. Tamponar TrichoSol™ con trietanolamina hasta pH 4-5 (aproximadamente un 3-4%).
2. Pesar la finasterida reducida previamente a polvo fino.
3. Incorporar 4% de Cremophor RH 40 hasta formar una pasta.
4. Incorporar poco a poco TrichoSol™.
5. Mezclar hasta homogeneización.
6. Envasar. Etiquetar "Agitar antes de usar".

Caducidad: 3 meses

Posología: 1 ml / 24 horas

Alopecia androgenética	
Minoxidil	5 %
Finasterida	1%
TrichoSol™ c.s.p.	100 ml

Modus operandi:

1. Pesar el minoxidil reducido previamente a polvo fino.
2. Situar 90 ml de TrichoSol™ en un vaso de precipitado y añadir el minoxidil.
3. Agitar hasta la completa disolución de minoxidil.
4. Pesar la finasterida reducida previamente a polvo fino.
5. Incorporar 4% de Cremophor RH 40 hasta formar una pasta.
6. Incorporar poco a poco la mezcla de TrichoSol™ y minoxidil.
7. Mezclar hasta homogeneización.
8. Enrasar y envasar. Etiquetar "Agitar antes de usar".

Caducidad: 3 meses

Posología: 1 ml / 24 horas

Conservación

En envase bien cerrado, protegido de la luz, T<25 °C.

Bibliografía

Información del fabricante.

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Fagron personalizing medicine

ANEXO III – FICHA DE PREPARAÇÃO DO MEDICAMENTO MANIPULADO

farmácia Luciano & Matos

FICHA DE PREPARAÇÃO DE MEDICAMENTOS MANIPULADOS

Medicamento: Minoxidil 5% em TrichoSol®

Teor em substância(s) activa(s); 100g (ml ou unidades) contêm 5 g (ml) de minoxidil.

Forma farmacêutica: solução **Data de preparação:** 22/04/2021

Número de lote: 20210413B **Quantidade a preparar:** 100 ml

Matérias-primas	Nº de lote	Origem	Farma-copeia	Quantidade para 100ml	Quantidade calculada	Quantidade pesada	Rubrica do operador	Rubrica do supervisor
Minoxidil	20061-Z-1	Acofarma	PhEur 10.1	5 g	5,031 g	5,031 g	Fátima	
TrichoSol®	0531820	Fagron	Fagron	q.b. p. 100 ml	q b p 100 mL	85 mL + 11 mL	Fátima	

Preparação

1. Verificar o estado de limpeza do material.	Fátima
2. Dissolver o minoxidil em cerca de 95 ml de TrichoSol®, executando a mistura no agitador magnético.	Fátima
3. Se houver problemas de solubilização, pode-se aquecer o TrichoSol sem ultrapassar os 50ºC durante uns minutos, até completa dissolução do minoxidil.	Fátima
4. Filtrar para uma proveta graduada e perfazer o volume final de 100 ml com TrichoSol®.	Fátima
5. Transferir a solução final para 1 frasco com spray doseador.	Fátima
6. Lavar e secar o material utilizado.	Fátima

Aparelhagem usada: Balança BL.01, Agitador magnético

Embalagem

Tipo de embalagem: Frasco de plastico com pulverizador Capacidade do recipiente: 125 mL

Material de embalagem	Nº de lote	Origem
Frasco PET	0107d0	Acofarma
—	—	—

Operador: Fátima

Prazo de utilização e Condições de conservação

Condições de conservação: Conservar na embalagem bem fechada e ao abrigo da luz, à temperatura ambiente

Operador: Fátima

Prazo de utilização: 90 dias

Operador: Fátima

Rotulagem

1. Proceder à elaboração do rótulo de acordo com o modelo descrito em seguida.
2. Anexar a esta ficha de preparação uma cópia, rubricada e datada, do rótulo da embalagem dispensada.

Modelo de rótulo

Identificação da Farmácia
Identificação do Director Técnico
Endereço e telefone da Farmácia

Identificação do Médico prescritor
Identificação do doente

DENOMINAÇÃO DO MEDICAMENTO

Teor em substância(s) activa(s)
Quantidade dispensada
Referência a matérias-primas cujo conhecimento seja eventualmente necessário para a utilização conveniente do medicamento
Posologia
Via de administração

Data de preparação
Prazo de utilização
Condições de conservação
Nº de lote
Manter fora do alcance das crianças
Advertências (precauções de manuseamento, etc.)
Uso externo (caso se aplique) (em fundo vermelho)

farmácia Luciano & Matos
Dir. Téc: Dra. Maria Helena Amado
Praça 8 de Maio, 40-42 | 3000-300 Coimbra
Telf: 239 822 147 | Fax: 239 824 112

Minoxidil 5%
TrichoSol®
q.b.p. 100 ml

Posologia: Aplicar 1 ml 2 vezes ao dia OU segundo indicação médica.
1 ml = 10 pulverizações

Preço: 36,15€
Aplicar sobre o couro cabeludo seco com uma ligeira massagem, até completa absorção.
Lavar as mãos após a aplicação.

Utente:
Conservar à temperatura ambiente, em local seco e fresco
Data Prep.: 22-04-2021
Manter fora do alcance das crianças

USO EXTERNO
Lote: 202104139
Prazo utiliz.: 22-07-2021

Operador: Fátima

Verificação

ENSAIO	ESPECIFICAÇÃO	RESULTADO	Rubrica do operador
Cor	Ligeiramente amarelado	Conforme	Fátima
Odor	Característico do TrichoSol®	Conforme	Fátima
Aspecto	Homogéneo	Conforme	Fátima
Quantidade	100 ml ± 5%	Conforme	Fátima
pH	Entre 4 e 5	Conforme (pH=4)	Fátima

Aprovado ☒ Rejeitado ☐

Supervisor: _____ 22/04/21

Nome e morada do doente

-

Nome do prescritor

—

Anotações

—

Cálculo do preço de venda

MATÉRIAS-PRIMAS:

Matérias-primas	Embalagem existente em armazém		Preço de aquisição de uma dada quantidade unitária (sem IVA)		Quantidade a usar	Factor multiplicativo	Preço da matéria-prima utilizada na preparação
	Quantidade adquirida	Preço de aquisição (s/ IVA)	Quantidade unitária	preço			
Minoxidil	100g	23,18 €	1g	0,2318 €	x 5,031	x 2,2	= 2,57 €
TrichoSol®	10,15g	39,78 €	1g	0,039 €	x 97,44	x 1,9	= 7,22 €
						Total Matéria-Prima (A)	= 9,79 €

HONORÁRIOS DE MANIPULAÇÃO:

	Forma Farmacêutica	Quantidade	F (€)	Factor multiplicativo	Valor
Valor referente à quantidade base	Solução	100 ml	5,05 €	x 3	= 15,15 €
Valor adicional		—	x — €	x —	= — €
				Total da Manipulação (B)	= 15,15 €

MATERIAL DE EMBALAGEM:

Materiais de embalagem	Preço de aquisição		Quantidade		Factor multiplicativo	Valor
Frasco pulverizador 125 mL	1,05	€	x 1		x 1,2	= 1,26 €
—	—	€	x —		x —	= — €
				Total de Material de Embalagem (C)		= 1,26 €

P. V. P. DO MEDICAMENTO MANIPULADO:

Soma de (A) + (B) + (C)	Factor multiplicativo	Valor
26,2 €	x 1,3	= 34,06 €
	I. V. A. (6%)	+ 2,04 €
	PVP	= 36,10 €

Operador: Fátima

Supervisor: _____

ANEXO IV – FICHA DE PREPARAÇÃO DO MANIPULADO EMITIDA PELO SISTEMA Pharma LM

farmácia Luciano & Matos

Dra. Maria Helena Amado
Praça 8 de Maio, 40-42 | 3000-300 Coimbra

Telf: 239 822 147/8
Email: laboratorio@cnca.pt

Ficha de Preparação 748

Minoxidil 5% em TrichoSol

Forma farmacêutica: Solução
Nº Lote: 202104139

Data de Preparação: 22-04-2021
Quantidade: 1 x 100 mL

Composição

Lote	ID	Nome	Origem	Qt unit (mg)	Qt Teorica	Unid	Qt Calc	Unid	Qt Total	Unid	Factor	Preço
200691-J-1	7	Minoxidil	Acofarma	0	5,00000 g		5,03068 g		5,03068 g		2,2	2,565 €
0531820	493	Trichosol	Fagron	0	97,44000 g		97,44000 g		97,44 g		1,9	7,256 €
			Sub-Total:	0	102,44		102,47068		102,47068			9,821 €

Embalagem

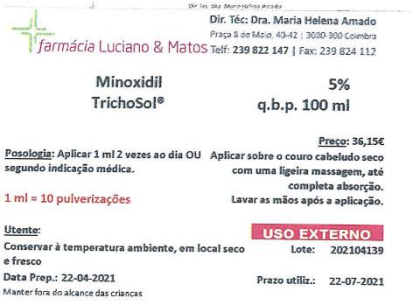
Lote	Nome	Qt	Preço
010720	Frasco plástico 125ml spray para minoxidil	1	1,260 €
	Sub-Total:		1,260 €

Operações prévias:

Verificar que a área laboratorial está limpa e desocupada;
Verificar se estão disponíveis todos os materiais, equipamentos e matérias-primas;
Proceder à preparação do manipulado, respeitando as Boas Práticas de Preparação de Manipulados;

Modo de Preparação:

1. Verificar o estado de limpeza do material.
2. Dissolver o minoxidil em cerca de 95 ml de TrichoSol® (para um volume final de 100 ml), executando a mistura no agitador magnético.
3. Se houver problemas de solubilização, pode-se aquecer o TrichoSol sem ultrapassar os 50ºC durante uns minutos, até completa dissolução do minoxidil.
4. Filtrar para uma proveta graduada e perfazer o volume final com TrichoSol®.
5. Transferir a solução final para 1 frasco com spray doseador.
6. Lavar e secar o material utilizado.



Dados de Identificação:

Utente

Médico

Controlo de Qualidade: Operador Mélanie Duarte

	Especificação	Resultado		Especificação	Resultado
Aspecto:	Homogéneo	Homogéneo	Unif de Massa:	NA	
Cor:	Ligeiramente amarelado	Ligeiramente amarelado	Transparência:	NA	
Odor:	Característico do TrichoSol	Característico do TrichoS	pH:	4-5	4-5

Operador: Supervisor: Registado por: Libertado por: Data Libertação:

748

farmácia Luciano & Matos
Dra. Maria Helena Amado
Praça 8 de Maio, 40-42 | 3000-300 Coimbra
Telf: 239 822 147/8
Email: laboratorio@cnca.pt

Ficha de Preparação 748

Minoxidil 5% em TrichoSol

Forma farmacêutica: Solução
Data de Preparação: 22-04-2021
Nº Lote: 202104139
Quantidade: 1 x 100 mL

Monografia:	Solução	Conforme	Qt. Final (+/- 5%)	100 mL	100 mL

Resultado CQ: **Aprovado** Hora/Data: 22-04-2021 16:50:10 Operador UM:

Observações: pH= 4

Cálculo do Preço:

Forma Farmacêutica	F	Factor	Limite	Factor adicional	Manipulação	Sub-Total
Solução	5,05	3	100	0,005	15,15 €	26,23 €

PVP calculado ao abrigo da Portaria nº 769/2004 de 1 de Junho — Iva 6 % — Preço sem IVA: 34,10 € — **PVP*: 36,15 €**

Operador: Supervisor: Registado por: Libertado por: Data Libertação:

748

RELATÓRIO DE ESTÁGIO EM INDÚSTRIA FARMACÊUTICA

- BLUEPHARMA – Indústria Farmacêutica, S.A. COIMBRA -

Assuntos Regulamentares

Sob a orientação da Dra. Catarina Madanêlo

Lista de Abreviaturas

ANVISA – Autoridade Nacional de Vigilância Sanitária

AR – Assuntos Regulamentares

DL – *Deficiency Letters*

EUA – Estados Unidos da América

FDA – *Food and Drug Administration*

FFUC – Faculdade de Farmácia da Universidade de Coimbra

GMP – *Good Manufacturing Practices*

MICF – Mestrado Integrado em Ciências Farmacêuticas

SWOT – *Strengths, Weaknesses, Opportunities, Threats*

1. Introdução

O Mestrado Integrado em Ciências Farmacêuticas (MICF) apresenta um plano de estudos bastante diversificado no qual os estudantes adquirem conhecimentos teóricos nas mais diversas áreas da saúde. Esta formação pretende transmitir-lhes s conhecimentos necessários para que, no futuro, sejam capazes de desempenhar o seu papel de farmacêuticos, quer seja atuando nas várias etapas do ciclo de vida do medicamento, desde a sua produção até à chegada ao público, quer seja noutras áreas , como por exemplo análises clínicas e análise de alimentos. Porém, a formação dos estudantes do MICF não estaria completa sem a realização de um estágio curricular no qual estes tivessem a oportunidade de contactar com o mundo do trabalho e assim pôr em prática os conhecimentos até então adquiridos.

Sendo o MICF caracterizado por um vasto leque de saídas profissionais, a Faculdade de Farmácia da Universidade de Coimbra (FFUC) dá a oportunidade aos seus alunos de estes realizarem estágio curricular em algumas das principais áreas profissionais do sector farmacêutico, nomeadamente a indústria farmacêutica.

A oportunidade de realizar este estágio curricular na Bluepharma surgiu através da apresentação de uma candidatura por parte dos alunos interessados, sendo esta seguida de uma entrevista na qual é feita a seleção de alunos para estagiar nesta empresa. Durante o processo de seleção, tive oportunidade de demonstrar o meu interesse pela área de Assuntos Regulamentares (AR), acabando por ser selecionada para realizar estágio nesta mesma área.

2. A Bluepharma

A Bluepharma é uma empresa farmacêutica portuguesa sediada em Coimbra. Deu início à sua atividade em fevereiro de 2001, após a aquisição de uma das unidades industriais da multinacional Bayer, por um grupo de profissionais do sector (Bluepharma, 2021).

Ao longo dos seus 20 anos de existência tem vindo a crescer passando de uma unidade industrial que empregava 58 funcionários e que operava apenas a nível nacional para um grupo farmacêutico constituído por 20 empresas e que emprega agora mais de 700 trabalhadores. Possui atualmente delegações em 4 países [Espanha, Angola, Moçambique e Estados Unidos da América (EUA)] (Bluepharma, 2021).

A atividade da Bluepharma foca-se na investigação, desenvolvimento e registo de medicamentos próprios; produção de medicamentos próprios e para terceiros; e comercialização de medicamentos genéricos, percorrendo toda a cadeia de valor do medicamento desde o desenvolvimento até à entrada no mercado (Bluepharma, 2021).

O grupo Bluepharma encontra-se em expansão no mercado farmacêutico, procurando o reconhecimento de mercados e autoridades mais exigentes. Recebeu, em 2009, certificação por parte da autoridade norte-americana do medicamento, a *Food and Drug Administration* (FDA), para o desenvolvimento e produção de formas sólidas, tornando-se assim na primeira empresa farmacêutica portuguesa a poder exportar os seus produtos para os EUA. Obteve também, em 2016, certificação por parte da autoridade regulamentar do Brasil, a Autoridade Nacional de Vigilância Sanitária (ANVISA), o que lhe abriu a porta para o mercado brasileiro (Bluepharma, 2021).

Deste modo o grupo Bluepharma apresenta-se como um dos mais empreendedores e inovadores no setor farmacêutico, conquistando enorme prestígio tanto no mercado nacional como também internacional.

Com os olhos postos no futuro, a Bluepharma desenvolveu um projeto designado "Bluepharma Acelera 2030" que tem o objetivo de, até 2030, criar novas instalações da empresa em Eiras, de forma a aumentar a capacidade tecnológica e recursos humanos e assim continuar o seu crescimento. Estas novas instalações vêm também possibilitar a produção de medicamentos que incorporam substâncias ativas de elevada atividade farmacológica. Sendo a Bluepharma caracterizada pela sua proatividade e dinâmica, este crescimento visa colocar a empresa em novos mercados, aumentar o número de empregos e reforçar a posição da Bluepharma como uma empresa farmacêutica de referência (Bluepharma, 2021).

3. Análise SWOT

3.1. Pontos Fortes (*Strengths*)

3.1.1. Condições e ambiente de trabalho

Um dos fatores críticos para o sucesso de uma empresa é a sua equipa. Por conseguinte, a Bluepharma preocupa-se com o bem-estar e satisfação dos seus colaboradores proporcionando-lhes ótimas condições de trabalho, como o fornecimento de todo o material necessário, desde computador e outros componentes eletrónicos a material de escritório e espaços especificamente designados para refeições dentro das instalações da empresa.

O ambiente de trabalho é um dos pilares para o bom funcionamento de uma equipa. No departamento de AR, tive o privilégio de me deparar com uma equipa bastante jovem, com um forte espírito de equipa, e, acima de tudo, de amizade, o que facilitou a minha integração.

3.1.2. Formação continua

A Bluepharma investe na formação dos seus colaboradores de modo a equipá-los com as ferramentas necessárias para que eles possam desempenhar as suas funções o melhor possível.

Quando iniciei o período de estágio, fiz também várias formações como, por exemplo, formação em "Melhoria Contínua", em "Sistema de Gestão Integrado e GMP", em "Ambiente e Segurança no Trabalho", entre outras, que me permitiram conhecer os protocolos de funcionamento da empresa e as suas políticas. Além destas formações iniciais transversais a todos os departamentos, existe uma formação contínua dos colaboradores, o que é bastante notório no departamento de AR, onde são regularmente realizadas apresentações de temas pertinentes para o departamento.

As formações ministradas pela Bluepharma foram para mim uma mais-valia, pois deram-me a oportunidade de conhecer a empresa bem como de adquirir novos conhecimentos, aplicando-os no contexto real da indústria farmacêutica.

3.1.3. Autonomia no desempenho das tarefas

Aquando da minha chegada à Bluepharma foram-me ministradas diversas formações para assim conhecer a empresa, e mais concretamente o departamento de AR. Após a realização dessas formações iniciais, passei então a executar as tarefas que me eram atribuídas, não só pela diretora do departamento, a Dra. Catarina Madanêlo, como também pelas restantes colegas. Destaco, entre estas tarefas, a criação de uma base de dados das taxas de registo de medicamentos a nível europeu, a criação de bases de dados de *Deficiency Letters* (DLs) e a preparação de respostas a DLs. Embora as colegas estivessem sempre disponíveis para me auxiliar, todas estas tarefas foram realizadas por mim de forma independente. No final, uma das colegas verificava somente se era necessário fazer alguma correção. Este método de trabalho foi bastante vantajoso, já que me permitiu trabalhar de forma autónoma, testando os meus conhecimentos. A confiança em mim depositada também me incentivou a realizar um trabalho cada vez melhor e a estar segura.

3.2. Pontos Fracos (*Weaknesses*)

3.2.1. Divisão do departamento em dois turnos e teletrabalho

Devido à atual situação pandémica, e de modo a evitar ajuntamentos, a equipa dos AR da Bluepharma encontrava-se, à altura do meu estágio, a trabalhar em dois turnos. Aquando da minha chegada à empresa foi-me dada a possibilidade de escolher entre realizar o estágio

em teletrabalho ou em regime misto, sendo integrada num destes turnos, tendo eu escolhido ficar a trabalhar em regime misto.

O facto de haver esta divisão do departamento em dois turnos impediu-me de conhecer pessoalmente algumas das colegas. Além do mais, a situação pandémica durante o decorrer do meu estágio agravou consideravelmente, tendo a equipa dos AR sido forçada a ficar em teletrabalho durante o mês de julho. Apesar de a Bluepharma dispor de várias plataformas de comunicação, e de as colegas estarem sempre prontas a ajudar esclarecendo qualquer dúvida, sinto que este regime de teletrabalho me privou de estabelecer relações mais próximas.

3.2.2. Duração do estágio

Considero que este estágio foi bastante importante para mim enquanto farmacêutica. No entanto, penso que três meses não sejam o tempo suficiente para conseguir verdadeiramente experienciar o que é trabalhar em AR. Por isso, apesar de todo o conhecimento que adquiri ao longo destes três meses, considero que a curta duração deste estágio me impediu de trabalhar em determinadas áreas de ARs, de realizar tarefas mais complexas e de perceber como funcionam determinadas plataformas utilizadas pela equipa dos AR.

3.3. Oportunidades (*Opportunities*)

3.3.1. Contacto com a indústria farmacêutica e com os vários mercados da mesma a nível mundial

A grande variedade de unidades curriculares lecionadas no MICF oferece aos seus estudantes inúmeras saídas profissionais, nomeadamente ao nível da indústria farmacêutica. Este estágio permitiu-me não só conhecer uma parte do vasto setor da indústria farmacêutica a nível nacional, como também conhecer um pouco do que é a indústria farmacêutica no mercado internacional, especialmente na Europa e EUA. Deu-me também a oportunidade de aprender a base geral de funcionamento dos procedimentos de registo nestes dois territórios.

3.3.2. Contacto com outros departamentos

Estando o departamento de AR constantemente em contacto com os outros departamentos da empresa, especialmente com o departamento da *Compliance*, tive a oportunidade de conhecer, de um modo geral, alguns departamentos e as suas respetivas funções. Considero esta interação vantajosa para mim na medida em que me permitiu

conhecer outras áreas dentro da indústria farmacêutica e expandir os meus horizontes, principalmente no que respeita a futuras possibilidades no mundo da indústria farmacêutica.

3.4. Ameaças (*Threats*)

3.4.1. Instalações separadas

A Bluepharma encontra-se em crescimento exponencial tornando-se impossível albergar todos os departamentos nas instalações iniciais da empresa, em São Martinho do Bispo. Assim sendo, a empresa inaugurou, em 2012, um novo pólo em Taveiro, sendo o departamento de AR transferido para a nova localização. Estando este departamento constantemente em contacto com os demais departamentos, esta divisão da empresa perturba o seu normal funcionamento, limitando a capacidade de resposta e a comunicação que são vitais para o cumprimento das suas funções. Para além do mais, este distanciamento pode ainda provocar limitações maiores no caso de falha nos sistemas de comunicação interna.

4. Conclusão

A indústria farmacêutica apresenta-se como uma área bastante diversificada em termos de saídas profissionais. Este estágio permitiu-me conhecer melhor o mundo da indústria farmacêutica e algumas das áreas que alberga bem como perceber a importância de um departamento de AR numa indústria farmacêutica.

O departamento de AR é o responsável por reunir toda a informação necessária ao registo dos medicamentos e, posteriormente, proceder ao seu registo. Assim sendo, está em constante contacto com os outros departamentos de forma a garantir que todos os critérios de qualidade necessários são cumpridos. É este departamento que mantém o contacto com os clientes e com as autoridades regulamentares, funcionando como elo de ligação entre ambos.

Concluo este estágio certa deste ter sido uma etapa importante no meu percurso académico, fornecendo-me ferramentas essenciais para o meu futuro enquanto farmacêutica. Considero que seria de extrema importância que todos os alunos do MICF tivessem a oportunidade de realizar um estágio em indústria farmacêutica de forma a conhecer esta realidade que tantas saídas profissionais oferece.

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MONOGRAFIA

"CANNABINOID-BASED THERAPIES FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM RELATED DISORDERS"

Sob a orientação do Professor Doutor Carlos Manuel Freire Cavaleiro

Abbreviation List

2-AG – 2-Arachidonoylglycerol

5-HT1A – 5-Hydroxytryptamine IA receptor

AD – Alzheimer's Disease

AEA – Anandamide

Aβ – beta Amyloid Peptide

$Ca2^{+}$ – Calcium Ion

CAMS – Study "Cannabinoids in MS"

CB1 – Cannabinoid Receptor 1

CB2 – Cannabinoid Receptor 2

CBD – Cannabidiol

CBDA – Cannabidiolic Acid

CBDV – Cannabidivarin

CBN – Cannabinol

CBR – Cannabinoid Receptor

CNS – Central Nervous System

DAGL – Diacylglycerol Lipase

DS – Dravet Syndrome

eCB – Endocannabinoid

ECS – Endocannabinoid System

EMA – European Medicines Agency

EU – European Union

FAAH – Fatty Acid Amide Hydrolase

FDA – Food and Drug Administration

FIRES – Febrile Infection-Related Epilepsy Syndrome

GPCR – G-protein Coupled Receptor

HD – Huntington Disease

LGS – Lennox-Gastaut Syndrome

MAGL – Monoacylglycerol Lipase

MDD – Major Depressive Disorder

MOVE 2 – Mobility Improvement 2 Studies

MS – Multiple Sclerosis

MUSEC – Study "MS and Extract of Cannabis"

NAPE – N-acyl-phosphatidylethanolamine

NAPE-PLD – N-acylphosphatidylethanolamine-phospholipase D

PANSS – Positive and Negative Symptom Scale

PD – Parkinson's Disease

RCTs – Randomized Clinical Trials

TRE – Treatment-Resistant Epilepsy

TRPV1 – Transient Potential Vanilloid Receptors Type 1

TSC – Tuberous Sclerosis Complex

USA – United States of America

Δ8-THC – Δ8-Tetrahydrocannabinol

Δ9-THC – Δ9-Tetrahydrocannabinol

Δ9-THCV – Δ9-Tetrahydrocannabivarin

RESUMO

A *Cannabis sativa* L. é há muito conhecida e utilizada pelo Homem, tanto para fins medicinais como não medicinais, tendo sido, por exemplo, utlizada como fonte de fibra na produção de velas para navios ou papel, ou ainda como alimento, devido às propriedades nutricionais do seu óleo. No entanto, devido à sua atividade psicotrópica o seu consumo foi, durante muitos anos, proibido sendo esta vista apenas como uma substância de abuso. A descoberta do Sistema Endocanabinoide no corpo humano nos anos 1990 veio mudar este paradigma, renovando o interesse pela canábis.

A canábis é uma espécie quimicamente complexa, capaz de produzir diversos compostos, sendo, os principais, os fitocanabinoides. Estes são capazes de interagir com os recetores canabinoides e modular a sua atividade. Os fitocanabinoides, especialmente o canabidiol e o Δ9-tetra-hidrocanabinol, têm demonstrado propriedades anti-inflamatórias e neuroprotetoras, entre outras, despertando assim o interesse como potenciais agentes terapêuticos em várias patologias, nomeadamente do sistema nervoso central, como a epilepsia, doenças neurodegenerativas e doenças do foro psicológico. Vários estudos têm sido realizados neste campo e os resultados têm sido bastante promissores.

O objetivo deste trabalho é compilar a informação existente e discutir a eficácia e segurança de terapias à base de derivados de canábis no tratamento de diversas patologias do sistema nervoso central.

Palavras-chave: Canábis, Canabidiol, Δ9-tetra-hidrocanabinol, Sistema Endocanabinoide, Sistema Nervoso Central.

ABSTRACT

Cannabis sativa L. has long been known and used by mankind, both for medicinal and non-medicinal purposes, for example, as a source of fiber in the production of sails for ships or paper, or as a food source, due to the nutritional properties of its oil. However, due to its psychotropic activity its consumption was, for many years, prohibited and cannabis was considered a substance of abuse. The discovery of the Endocannabinoid System within the human body in the 1990s changed this paradigm, renewing interest in cannabis.

Cannabis is a chemically complex species, capable of producing several compounds, the major ones being the phytocannabinoids. These are capable of interacting with cannabinoid receptors and modulate their activity. Phytocannabinoids, especially cannabidiol and Δ9-tetrahydrocannabinol, have demonstrated anti-inflammatory and neuroprotective properties, among others, thus arousing interest as potential therapeutic agents in various pathologies, including pathologies of the central nervous system, such as epilepsy, neurodegenerative diseases, and psychological disorders. Several studies have been carried out in this field and the results have been very promising.

The objective of this work is to gather the existing information and to discuss the effectiveness and safety of cannabinoid-based therapies in the treatment of various pathologies of the central nervous system.

Keywords: Cannabis, Cannabidiol, Δ9-tetrahydrocannabinol, Endocannabinoid System, Central Nervous System.

1. Introduction

The Endocannabinoid System (ECS) modulates neuronal activity having a very important role in the coordination of various neurobiological processes such as memory and learning, cognition, motor behavior, nociception, among others (Fernández-Ruiz *et al.*, 2020). Therefore, the dysregulation of the ECS is associated with many pathologies of the Central Nervous System (CNS), such as epilepsy, neurodegenerative disorders, and psychiatric disorders (Cristino, Bisogno e Di Marzo, 2020).

Consequently, molecules that modulate the ECS, such as, cannabinoid receptor antagonists and agonists, can be valuable in the treatment of specific diseases within the neuropsychopharmacology field (Cristino, Bisogno e Di Marzo, 2020; Fernández-Ruiz *et al.*, 2020).

Cannabis sativa L. (hereafter referred to as cannabis) is an annual flowering herb of the Cannabaceae family that contains over 500 natural compounds, of which more than 100 have been designated as phytocannabinoids (Amin e Ali, 2019; Barcaccia *et al.*, 2020; Pisanti e Bifulco, 2019). Many phytocannabinoids, including Δ9-tetrahydrocannabinol (Δ9-THC), and cannabidiol (CBD) have shown potential to modulate receptors, such as cannabinoid receptors (CBRs), ionotropic channels, and enzymes related to the ECS (Sampson, 2021).

This has led to several studies investigating the potential effects of cannabis and cannabinoid-based therapies in the treatment of CNS pathologies.

2. Historical Perspective

The history of cannabis goes alongside the history of humankind. Cannabis has been extensively used for many purposes beyond its psychotropic effect such as medicinal and non-medicinal purposes for thousands of years (Foster, Abramovici e Harris, 2019; Pisanti e Bifulco, 2017).

Several academics speculate that cannabis appeared during the Pleistocene Epoch, millions of years ago. Asia seems to be the first place where it was exploited. It was used for medicinal and ritualistic purposes and as a fiber and food source. Its use in traditional medicine is recorded in the most ancient Chinese Pharmacopoeia, Shen Nung's "Pen Ts'ao Ching". Due to the restrictions established by the Chinese empire, cannabis started to leave China heading for India and towards the West (Pisanti e Bifulco, 2019).

The modern history of medical cannabis starts in the 19th century with the Irish physician William Brooke O'Shaughnessy who diffused among the European medical

community the innumerable pharmacological benefits of cannabis. O'Shaughnessy realized that the Indian varieties of cannabis, which he named *Cannabis indica*, showed better medicinal properties than the ones spotted in Europe, *Cannabis sativa*. The interest in this new strain of cannabis, and particularly its resin - "hashish", rapidly increased and spread across Europe. The second half of the 19th century is, without doubt, the golden age of cannabis in medicine. However, the use of medical cannabis began to decline at the beginning of the 20th century. Multiple were the reasons at the basis of such fall, but the most evident was the remarkable variability in both efficacy and therapeutic doses amongst patients, as the pharmacologically active compounds were not quantified (Pisanti e Bifulco, 2019, 2017). Furthermore, the use of cannabis for recreational purposes became popular, which led to its condemnation. Nonetheless, scientific research on cannabis was pursued in several countries, and, in 1964, the Israelite scientists Gaoni and Mechoulam, identified for the first time the chemical structure of Δ9-THC. This finding encouraged the studies on the characterization of cannabis to continue and in the 1990s the ECS was discovered. The mindset about the therapeutic value of cannabis is changing throughout the world with a return to the past. Medical cannabis is now receiving heightened attention from patients, physicians, and governments. Meanwhile, in the last years, several countries have acquired new more permissive policies towards cannabis, approving laws that allow its medical use and decriminalizing or even legalizing its recreational use (Pisanti e Bifulco, 2019, 2017).

3. Why Cannabis has been valued recently

Due to its narcotic properties, *Cannabis sativa* was globally classified as a substance of abuse for most of the 20th century. This caused the scientific research to focus on the harms associated with the use of cannabis, instead of its supposed therapeutic properties (Sampson, 2021).

However, in the past 15-20 years the interest in cannabis as a therapeutic agent was renewed (Amin e Ali, 2019). This arose from the discovery of the ECS, which unraveled the importance of cannabinoids in the human body. Until this moment cannabis was considered a substance of abuse with no therapeutic value, but the discovery of the CBRs and the characterization of the endocannabinoids (eCBs) and ECS changed the mindset about cannabis. The scientific interest in cannabis was renewed and thousands of papers supporting the therapeutic value of this plant were published, and thus far the results have been promising (Pisanti e Bifulco, 2017). There have also been some reports given by patients who noticed an improvement of their condition when using cannabis that contribute to this popularity of

therapeutic cannabis. In turn, this has led many countries to decriminalize the use of cannabis and establish programs for access to cannabis for medical purposes (Sampson, 2021).

Beyond the medicinal properties of cannabis, recently there has been an increasing interest in taking care of ourselves in a more natural way, which draw attention to the use of cannabis for cosmetic, and nutraceutical purposes (Pisanti e Bifulco, 2019).

The cannabis business is spreading throughout the world mostly due to its proposed medical benefits. Health care professionals are now concerned about the legality, efficacy, and safety of cannabinoid-based therapies. Therefore, the establishment of specific regulations is crucial to prevent any harm (Hawes *et al.*, 2020; Pisanti e Bifulco, 2019).

4. Legal situation of Cannabis throughout the world

The two main agencies responsible for drug evaluation and approval are the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA).

4.1. EMA and the European Union (EU)

Even though the EU provides a framework within which drug policies must operate, each member state has ultimate control over its drug policy, with European agencies only interfering if their contributions are considered of value to national efforts. Therefore, national drug policies are quite different across European countries. Some countries have prohibiting policies whilst others have loosened their tolerance towards the use of cannabis. For instance, the Netherlands has practiced the decriminalization of marijuana since the 1970s by establishing a system of coffee shops where the use and sale of cannabis is tolerated at a small scale. In 2001, Portugal decriminalized the use of recreational cannabis, and a new wave of liberalization swept across Europe. Belgium, decriminalized cannabis in 2003, while Estonia decriminalized the personal possession of all drugs in 2002, followed, more recently, by Poland and the Czech Republic (Chatwin, 2017). Regarding the use of cannabis for medicinal purposes, only Germany provides health insurance for cannabinoid-based therapies and only the Netherlands allows the use of the cannabis flower for medicinal purposes (Hall *et al.*, 2019).

The main cannabinoid-based medicines currently approved in European territory are Sativex® and Epidyolex®. Sativex® is an oromucosal spray formulated from extracts of *Cannabis sativa* that contains Δ9-THC and CBD. It is commonly used in the treatment of multiple sclerosis associated spasticity, and its use has been authorized in several member states of the EU (Abuhasira, Shbiro e Landschaft, 2018). Epidiolex® is a CBD-based medicine that was approved by EMA in 2019 as an orphan medicine for the treatment of seizures associated with

two rare and severe forms of epilepsy, Lennox-Gastaut Syndrome (LGS) and Dravet Syndrome (DS) (EMA, 2021).

4.1.1. Portugal

Until 2001 the recreational use of cannabis in Portugal was prohibited. According to Article 40 of the Decree-Law no. 15/93 anyone who consumed or, for their consumption, cultivated, acquired, or held cannabis plants, could be punished with a prison sentence of up to 3 months (República Portuguesa, 1993). However, in June 2001 Law no. 30/2000 came to revoke Article 40 of the Decree-Law no. 15/93 (except with regard to cultivation) and legalized the recreational use of cannabis in Portugal (República Portuguesa, 2000). The medicinal use of cannabis, in Portugal, namely its prescription and dispensation in pharmacies, is regulated by Law no. 33/2018, of July 18. Furthermore, the prescription of cannabis-based drugs, preparations, and substances is done through special prescription, and can only be carried out if conventional treatments with authorized medicines do not produce the expected effects or cause relevant adverse effects. It should also be noted that, in Portugal, medicines, preparations, and substances based on the cannabis plant, like all medicines, are always subject to an authorization issued by INFARMED - National Authority for Medicines and Health Products, IP (República Potuguesa, 2018).

4.2. FDA and the United States of America (USA)

Presently, in the USA, cannabis is marketed in three categories: "pharmaceutical" at the federal level and "medical" and "recreational" at the state level (Hawes *et al.*, 2020).

FDA is the responsible for the regulation of the products that claim medical properties, including cannabis-based products (Hawes *et al.*, 2020). FDA has approved 4 cannabis-based medicines, Cesamet®, Marinol®, Syndros®, and, more recently, Epidiolex® (Abuhasira, Shbiro e Landschaft, 2018; FDA, 2021). Cesamet® was approved as oral capsules containing 1 mg of nabilone (synthetic analog of Δ9-THC), for the treatment of nausea and vomiting caused by chemotherapy treatments, refractory to other therapies. Marinol® and Syndros® (dronabinol - Δ9-THC synthetic analog) were approved as oral capsules of 2.5; 5 and 10 mg and oral solution of 5 mg/mL, respectively. Their main indications are anorexia in patients with Acquired Immunodeficiency Syndrome, and nausea and vomiting associated with chemotherapy, refractory to other therapies (Abuhasira, Shbiro e Landschaft, 2018; Cristino, Bisogno e Di Marzo, 2020; FDA, 2021;). Epidiolex® (CBD) was originally approved in 2018 for the treatment of seizures associated with two rare and severe forms of epilepsy, LGS, and DS,

and, in 2020, was approved for the treatment of seizures associated with Tuberous Sclerosis Complex (TSC), in patients older than 1 year (FDA, 2021).

Cannabis was listed as a Schedule I drug in 1970, and its use was forbidden for any purpose. However, since then, several states have issued laws of their own, allowing the use of medical cannabis to some extent. California was the first state to legalize the use of medicinal cannabis in 1996 (Abuhasira, Shbiro e Landschaft, 2018). After that, more than 30 jurisdictions in the USA have legalized the use of cannabis for medicinal purposes. Regarding the recreational use of cannabis some states of the USA have already legalized commercial production of cannabis for recreational purposes (Hall *et al.*, 2019).

4.3. The future of Cannabis throughout the world

Recently, there has been a considerable change in drug policies and more countries are authorizing the use of cannabis for medical and recreational purposes. However, legalization is still in its early stages, because of the concerns about addiction and adverse events as well as the lack of evidence regarding the efficacy and safety of cannabis cause many countries to be prudent about their cannabis regulations (Abuhasira, Shbiro e Landschaft, 2018).

The liberalization of cannabis may be beneficial and lead to the decrease of the cannabis illicit market, but it is a very delicate process that needs to be carried out cautiously. After the legalization, governments should take measures to prevent harm, and educate people about these products, particularly about their benefits and their risks, so they can make an informed choice.

5. Characterization of *Cannabis sativa*

The cannabis plant is a dicotyledonous, apetalous wind-pollinated annual flowering herb of the Cannabaceae family. Normally cannabis is a diecious plant, with male and female flowers developing in separate plants, however, in rare cases, it can develop as an hermaphrodite, with both male and female flowers on the same plant (Barcaccia *et al.*, 2020; ElSohly *et al.*, 2017; Klumpers e Thacker, 2019). The exact number of cannabis existing species is controversial. Some botanical taxonomists claim there are three species with distinct phenotypic differences: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. However, despite that classification, cannabis is commonly treated as a monotypic genus, *Cannabis sativa* L., with different varieties: var. *sativa*, var. *indica*, and var. *ruderalis* (ElSohly *et al.*, 2017; Hurgobin *et al.*, 2021). The *sativa* and *indica* varieties are the most economically important and widespread, with the *sativa*

variety being the predominant in western society. These two varieties can be separated by morphology. The plants belonging to the *sativa* variety can reach up to 3.5 m and have a fibrous stalk, whereas the plants belonging to the *indica* variety only grow to an average height of 1.8 m and present a woody stalk. Also, the var. *indica* plants are bushier with broader and darker green leaves. As for the *ruderalis* variety, it is almost only cultivated in the region of the Himalayas, and it rarely is grown for its drug content. The *ruderalis* variety plants are plants who exhibit one or more of these characteristics: CBD and Δ9-THC similar contents, wild-type morphology and, early flowering (Amin e Ali, 2019; ElSohly *et al.*, 2017; McPartland, 2018).

Figure 1| Leaves of *Cannabis sativa* and *Cannabis indica.*

Cannabis sativa presents various chemotypes, or chemical phenotypes, with different cannabinoid profiles (Amin e Ali, 2019). Cannabis plants can be divided into three main chemotypes based on the Δ9-THC/CBD ratio:

- Type I (drug-type): Δ9-THC - predominant, (Δ9-THC/CBD $\gg$ 1);
- Type II (intermediate-type): contains both Δ9-THC and CBD in almost equal amounts, (Δ9-THC/CBD $\approx$1);
- Type III (fiber-type or hemp): CBD-predominant, (Δ9-THC/CBD $\ll$ 1).

Beyond these chemotypes, there are other chemotypes that express high concentrations of less known phytocannabinoids (Amin e Ali, 2019; Lewis, Russo e Smith, 2018). Chemotypes are very important, especially when cultivating cannabis for medicinal purposes, because depending on the presence, or absence, of certain cannabinoids, that is, the chemotype, cannabis will have different actions (Amin e Ali, 2019).

Cannabis is a chemically complex species that produces several different compounds that are then excreted by the trichomes concentrated around the female flowers as a resin (ElSohly *et al.*, 2017; Klumpers e Thacker, 2019). The number of compounds identified in the cannabis plant has increased over the years (ElSohly *et al.*, 2017). Until now, approximately 540 natural compounds of 18 different chemical classes including terpenes, flavonoids,

alkaloids, and phytocannabinoids have been identified (Amin e Ali, 2019; Foster, Abramovici e Harris, 2019).

The main constituents of cannabis are cannabinoids (Foster, Abramovici e Harris, 2019). Cannabinoids are fatty compounds that exhibit a typical C_{21} terpenophenolic skeleton, characteristic of cannabis plants even though some of them can be found in other plants (ElSohly *et al.*, 2017; Klumpers e Thacker, 2019). Cannabinoids obtained from the cannabis plant are usually called phytocannabinoids (Hawes *et al.*, 2020). Phytocannabinoids are secondary metabolites produced by the capitate-stalked glandular trichomes present in the female flowers of cannabis plants. Since the beginning of the chemical investigations on *C. sativa*, more than 100 phytocannabinoids have been isolated from this plant (ElSohly *et al.*, 2017; Hurgobin *et al.*, 2021). However, most of them have still not been tested for pharmacological activity (Sampson, 2021).

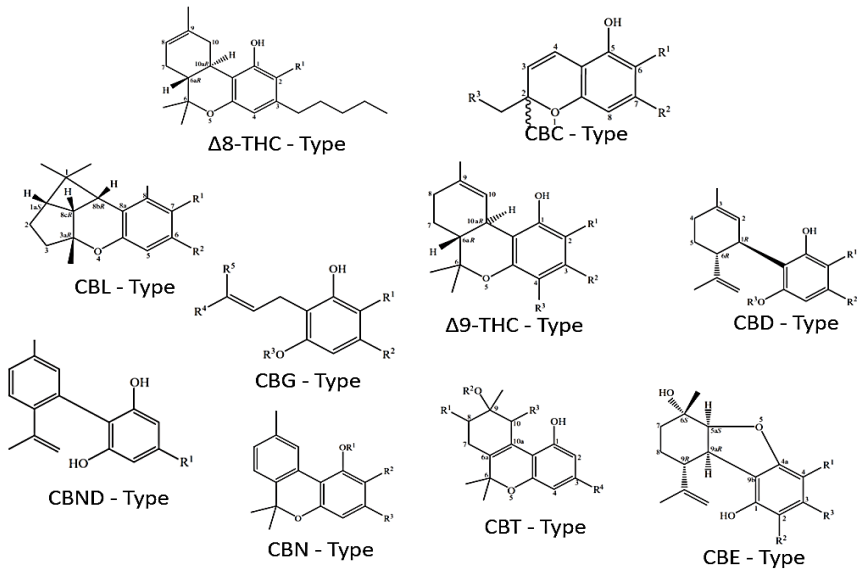

Figure 2| Different types of cannabinoids (cannabinodiol (CBND) type, cannabicyclol (CBL) type, (−) - Δ8-trans-tetrahydrocannabinol (Δ8-THC) type, (−) - Δ9-trans-tetrahydrocannabinol (Δ9-THC) type, cannabigerol (CBG) type, cannabinol (CBN) type, cannabichromene (CBC) type, cannabidiol (CBD) type, cannabielsoin (CBE) type, cannabitriol (CBT) type). Adapted from Sampson (2021).

The most relevant, well-studied and most abundant cannabinoids are Δ9-THC and CBD:

- **Δ9-THC**

The chemical structure and absolute configuration of Δ9-THC was first reported by Gaoni and Mechoulam, in 1964 (Pisanti e Bifulco, 2017). Δ9-THC is the main psychoactive metabolite present in cannabis, and the primary responsible for its narcotic effect. This effect is normally associated with the activation of the cannabinoid receptor 1 (CB1) - a receptor

highly expressed in the brain - by this molecule, which induces euphoria, anxiety, and paranoia. Nevertheless, Δ9-THC also shows therapeutic benefits, for example, by acting as an anti-inflammatory due to its interaction with the cannabinoid receptor 2 (CB2) - a receptor found predominantly in immune cells (Hurgobin *et al.*, 2021; Maroon e Bost, 2018).

- **CBD**

CBD is an isomer of Δ9-THC that was first isolated in 1940 by Adams *et al.*, however, its synthesis and absolute configuration were only determined in 1969 by Petrzilka *et al.* (ElSohly *et al.*, 2017). It is the main non-psychotropic metabolite present in *C. sativa* and a biologically active compound with a complex pharmacokinetic and pharmacodynamic profile. It can interact with CB1 and CB2 receptors, however, it presents low affinity for both of them. Nonetheless, this is just one of many pathways by which CBD exerts its effects. CBD is also capable of interacting with non-cannabinoid receptors, such as, enzymes, cellular uptake proteins, and transporters (ElSohly *et al.*, 2017; Maroon e Bost, 2018). For instance, CBD is an agonist of the transient potential vanilloid receptors type 1 (TRPV1) leading to pain-relief and anti-inflammatory effects. CBD can also act as an agonist of the 5-hydroxytryptamine (5-HT)1A receptors and modulate oxidative stress, brain excitotoxicity, and inflammation. Furthermore, the effect of CBD on serotonin receptors has antianxiety and anti-nausea properties (Fiani *et al.*, 2020).

6. The Endocannabinoid System

The discovery of specific membrane receptors for Δ9-THC, the CBRs, and consequent discovery of the eCBs, anandamide (AEA) and 2-arachidonoylglycerol (2-AG) and the enzymes involved in their biosynthesis and degradation, led to the identification of a new signaling system within the human body, the ECS. Thus, the ECS is the ensemble of the CB1 and CB2 receptors, the eCBs and the enzymes responsible for the biosynthesis and degradation of eCBs. However, this system is much more complex, being influenced by the overlap with other pathways, promiscuity of mediators, and alternative metabolic processes. Therefore, the modulation of its components affects a broader eCB-related network, the endocannabidiome (Cristino, Bisogno e Di Marzo, 2020).

The ECS is involved in diverse cellular and systemic pathways (Sampson, 2021). Its primary function is to regulate the homeostasis of the body by acting as a neuromodulatory system, especially during illness (Klumpers e Thacker, 2019). It is involved in several physiological processes, such as energy balance, appetite stimulation, nausea and vomiting

control, blood pressure, pain relief, embryogenesis, memory and learning and, immune response, among others (Fraguas-Sánchez e Torres-Suárez, 2018). Alterations in the ECS disrupt the physiological homeostasis and seem to be related with several diseases, which suggests that targeting components of the ECS is a possible therapeutic strategy for these cases (Cristino, Bisogno e Di Marzo, 2020; Fraguas-Sánchez e Torres-Suárez, 2018).

6.1. Cannabinoid receptors

The CB1 receptor was cloned for the first time in 1990 (Matsuda *et al.*, 1990). The translated genetic sequence generated a G-protein coupled receptor (GPCR) that showed cannabinoid selectivity. Three years later, a second type of cannabinoid GPCR, the CB2 receptor, was cloned from a human promyelocytic leukemia cell line (HL60) (Amin e Ali, 2019). To this moment two cannabinoid receptors have been identified, although there is debate about the existence of additional CBRs (Klumpers e Thacker, 2019).

The CB1 receptors are predominantly expressed in the CNS, especially in the cerebral cortex, nuclei basales, hippocampus, and cerebellum, in fact the CB1 receptor is the most abundant GPCR in the brain (Klumpers e Thacker, 2019; Li *et al.*, 2020a). However, CB1 receptors can also be found in peripheral nerve terminals and non-neuronal tissues like the uterus, prostate, testis, stomach, vascular endothelium, and skeleton (Fraguas-Sánchez e Torres-Suárez, 2018). CB1 receptors regulate several physiological processes, such as energy balance and metabolism, neuromodulation, learning and memory, and pain regulation (Li *et al.*, 2020a). Therefore, CB1 receptors as drug targets have been extensively studied, and have shown therapeutic applications in multiple disorders, including neuropathic and inflammatory pain, multiple sclerosis, Alzheimer's disease, anxiety, depression, obesity, liver fibrosis, and substance abuse disorders. However, the CB1 receptors are expressed on several different cells, which can lead to off-target effects that, in turn, will result in side effects. An example is the CB1 receptor antagonist Rimonabant, used for the treatment of obesity, that was withdrawn from the market due to serious psychiatric side effects (Li *et al.*, 2020a; Sampson, 2021).

The CB2 receptors are primarily expressed in cells of the immune system but can also be found in the CNS - but not in nerve cells, only in glial cells - especially under certain circumstances, such as in inflammation (Fraguas-Sánchez e Torres-Suárez, 2018). The activation of CB2 receptors induces the release of proinflammatory cytokines and migration of leukocytes. Therefore, they are considered good drug targets for autoimmune and inflammatory diseases (Li *et al.*, 2020a; Sampson, 2021).

It should also be taken into consideration that some effects of cannabinoids are mediated by non-cannabinoid receptors like the GPR55, transient receptor potential ion channels, serotonin (5-HT1A) receptors, and peroxisome proliferator-activated receptors (Britch, Babalonis e Walsh, 2021; Fraguas-Sánchez e Torres-Suárez, 2018; Sampson, 2021).

6.2. Endocannabinoids and enzymes responsible for their biosynthesis and degradation

eCBs are chemical compounds derived from fatty acid amides and diacylglycerols, that mammals produce in response to elevated intracellular calcium levels ($[Ca^{2+}]$ i). The main eCBs are AEA and 2-AG. AEA is produced through the hydrolysis of N-acyl-phosphatidylethanolamine (NAPE), which is catalyzed by the enzyme N-acyl-phosphatidylethanolamine-phospholipase D (NAPE-PLD), whilst the biosynthesis of 2-AG is catalyzed by diacylglycerol lipase (DAGL). Nonetheless, AEA and 2-AG can be synthesized through several other pathways and by different enzymes. Therefore, the inhibition of NAPE-PLD and DAGL enzymes might not always be effective in reducing the levels of AEA and 2-AG. The main enzymes related to the degradation of the AEA, and 2-AG are fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively, with other enzymes also participating in a lesser extent (Cristino, Bisogno e Di Marzo, 2020; Patricio *et al.*, 2020).

6.3. ECS and neuromodulation

The ECS has a critical role in the modulation of several synapses at the CNS, and eCBs are considered key regulators of synapse homeostasis. eCBs act as retrograde transmitters, which means, they are released from the postsynaptic terminal through a Ca^{2+}-dependent mechanism and travel retrogradely across the synapse to the presynaptic neuron where they activate the CB1 receptors, inhibiting the release of neurotransmitters. Therefore, this physiological mechanism controls the release of neurotransmitters and consequently the activation of their postsynaptic receptors, maintaining an adequate synaptic homeostasis, preventing, the excessive stimulation at excitatory or inhibitory synapses that leads to disease states (Fernández-Ruiz *et al.*, 2020; Lu e Mackie, 2021).

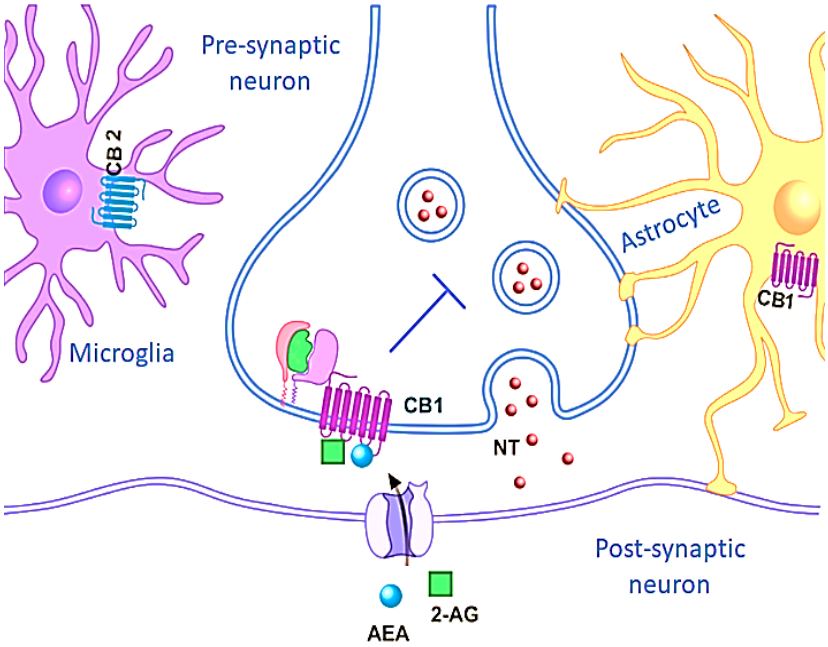

Figure 3 | Schematic representation of the synaptic modulation exerted by the ECS. The cannabinoid receptors are located in presynaptic terminals of glutamatergic, GABAergic, serotonergic, dopaminergic, and noradrenergic neurons. Therefore, eCBs act as retrograde transmitters, being released from the postsynaptic cell and acting on the presynaptic cell. Once in the synaptic space, the eCBs bind to their specific receptors, activating them. The CB1 receptors are GPCRs, that is, proteins with transmembrane domains coupled to inhibitory G-proteins that when activated acquire different conformations. The activation of CB1 receptors leads to the inhibition of adenylyl cyclase, and the inhibition of voltage dependent Ca2+ channels, that consequently decreases the release of presynaptic NT, (Patricio et al., 2020; Sampson, 2021). Abreviations: 2-AG, 2-arachidonoylglycerol; AEA, Anandamide; CB1, Cannabinoid Receptor 1; CB2, Cannabinoid Receptor 2; eCBs, Endocannabinoids; GPCRs, G-protein Coupled Receptors; NT, Neurotransmitters. Adapted from Patricio et al. (2020).

Phytocannabinoids can also act as retrograde transmitters inhibiting excitatory and inhibitory transmission in the CNS through the activation of presynaptic CB1 receptors (Maroon e Bost, 2018).

Even though eCBs act mainly as retrograde transmitters it is important to appreciate that they can also modify neuronal excitability in other ways. For instance, eCBs can directly modulate ion channels (including GABA-A, TRPV1, 5HT3, and glycine), and enhance hyperpolarization-activated cation channels (Lu e Mackie, 2021).

The communication between neurons, astrocytes and endocannabinoid elements also plays an important role in CNS modulation. Astrocytes, among other glial cells, process and control synaptic information and participate in synaptic plasticity. For instance, the CB1 receptors located on astrocytes have a very important role in neuro-glial communication. Furthermore, astrocytes express enzymes that metabolize eCBs, such as FAAH, which enables them to participate in eCB inactivation during retrograde signaling (Fernández-Ruiz *et al.*, 2020).

7. Cannabinoid-based therapies for the treatment of CNS related disorders

The ECS is involved in multiple neurobiological processes and if it becomes dysregulate it might contribute to the development of CNS diseases. Several endocannabinoid elements, particularly the CB1 receptors, are in abundance in CNS structures and it is becoming evident that the modulation of such elements may be valuable in the treatment of specific diseases within the neuropsychopharmacology field (Fernández-Ruiz *et al.*, 2020; Maroon e Bost, 2018).

7.1. Epilepsy

Epilepsy is a chronic neurological disorder in which there is an increase in the electrical activity of the neuronal networks in some areas of the brain. It can manifest as muscle contractions, brief episodes of absence, or prolonged and severe seizures. Seizures can be caused by prenatal lesions, genetic factors, developmental disorders, or brain diseases. Although, there are many cases where the cause of epilepsy cannot be identified (Fernández-Ruiz *et al.*, 2020; O'Connell, Gloss e Devinsky, 2017). Epilepsy affects nearly 65 million people worldwide, and approximately 30% of the individuals suffering from epilepsy are resistant to the drug therapies currently available (Amin e Ali, 2019). Treatment-resistant epilepsy (TRE) is defined as a failure to achieve sustained seizure control after the use of at least two antiepileptic drugs. All epilepsies can be resistant to treatment, nonetheless, epilepsy associated with Tuberous Sclerosis Complex (TSC), Lennox-Gastaut Syndrome (LGS), Dravet Syndrome (DS), and Febrile Infection-Related Epilepsy Syndrome (FIRES) are four of the most refractory to medical therapies. The available antiepileptic drugs are only partially successful in controlling seizures in TREs. Even though some antiepileptic drugs are capable of reducing seizure frequency in DS and LGS, there are limits to their safety and efficacy. TREs have significant repercussions, especially when they start in the first years of life because they might cause cognitive, behavioral, and motor delays. Patients struggling with TREs often suffer from both severe morbidity and increased mortality. Even epileptic patients who respond to therapy can have side effects and seizures. Most epilepsy patients, present a decreased quality of life due to both the disease and therapies used to control the seizures, also these therapies represent heavy costs to the healthcare systems (O'Connell, Gloss e Devinsky, 2017). Therefore, there is a significant need for effective and safe therapies capable of controlling TREs.

It has long been thought that cannabis can ameliorate convulsions, epileptic seizures, and spasticity (Amin e Ali, 2019). Reports of marijuana use in the treatment of epilepsy date back to 1800 BC (Maroon e Bost, 2018) and, more recently the ECS has been proposed to

participate in seizure control (Fernández-Ruiz *et al.*, 2020). Considering the potential role of the ECS in seizure management and the ability of some cannabinoids to control this, multiple preclinical studies have been performed. Studies in preclinical models of acute epilepsy usually involve treatment with substances such as kainic acid and pentylenetetrazol, or the enforcement of electric shocks to induce strong neuronal depolarization. The treatment with pilocarpine can also induce true status epilepticus in rodents (Cristino, Bisogno e Di Marzo, 2020). In a study conducted in 2003, Marsicano and co-workers demonstrated that the hippocampal levels of AEA increased after the occurrence of seizures in a preclinical model of acute epilepsy induced by kainic acid, while the levels of 2-AG remained unaltered. This suggests a possible role of the ECS in the protection against kainic acid-induced excitotoxicity (Marsicano *et al.*, 2003). Although, other authors have noticed significantly higher levels of 2-AG in the hippocampal region in rat pilocarpine models of epilepsy (Wallace *et al.*, 2003). The inhibition of eCB degrading enzymes, FAAH and MAGL, which increases AEA, and 2-AG levels also reduced the excitotoxic damage produced by kainic acid (Naidoo *et al.*, 2012). These data support the role of eCBs as a protective mechanism against the neurotoxic damage induced by seizures. In another study by Shirzadian *et al.*, published in 2018, acute foot shock stress was used as an acute stress to reduce seizure susceptibility in pentylenetetrazol-induced seizures in mouse models. The results obtained showed that blocking the CB1 receptors prevented the anticonvulsant effect of acute foot shock stress at doses from 1 pg/kg to 100 μg/kg (Shirzadian *et al.*, 2018). Also, other authors demonstrated that in animals subjected to acute epilepsy protocols upon treatment with WIN55,212-2 and ACEA, which are synthetic agonists of CB1 receptors, the seizure threshold increased (Bahremand *et al.*, 2009; Luszczki *et al.*, 2011). In a study published in 2003, Wallace *et al.* showed that the administration of Δ9-THC in rat models significantly decreased seizures induced by kainic acid, which involve CB1 receptors (Wallace *et al.*, 2003). This suggests that direct agonism of the CB1 receptors might be a good alternative in the treatment of epilepsy. Phytocannabinoids whose anticonvulsant effect does not rely on the activation of CB1 receptors, such as CBD, Cannabidivarin (CBDV), Cannabinol (CBN) and Cannabidiolic Acid (CBDA), have also been studied for the treatment of epilepsy, especially in TREs (Fernández-Ruiz *et al.*, 2020). Studies performed so far show that CBDV decreases seizures in a broad range of rodent models without affecting normal motor function (Fraguas-Sánchez e Torres-Suárez, 2018). Furthermore, in a study published in 2013, Amada *et al.* demonstrated that the suppression of several genes (Fos, Egr1, Arc, Ccl4, and Bdnf) associated with seizure induction in the CBDV respondent group of a pentylenetetrazol-induced seizure model led to a reduction in seizure severity (Amada *et al.*,

2013). Unlike Δ9-THC, the anticonvulsant action of CBDV seemed to be mediated by non-cannabinoid receptors, specifically by TRPV1 (Fraguas-Sánchez e Torres-Suárez, 2018).

Regarding clinical studies, most of the studies performed so far focus on the use of oral cannabis extracts, especially in cases of child epilepsy. For instance, in a study published in 2013 Porter and Jacobson reported that the oral administration of cannabis extracts rich in CBD as an add-on therapy in children with TREs diminished the frequency of seizures in 84% of the examined patients. Also 2 of the 16 responding patients became seizure-free after more than 4 months and 8 of the remaining 14 responding patients experienced a reduction in seizures superior to 80%. An improvement in behavior, sleep, and alertness was also noticed (Porter e Jacobson, 2013). An observational, longitudinal study by Hausman-Kedem *et al.* conducted between March 1, 2014, and June 30, 2016, examined the antiepileptic effect of CBD-enriched cannabis in children and adolescents with TREs. This study reported that the treatment with an oil with a CBD/THC ratio of 20:1 as an add-on therapy reduced mean monthly seizure frequency by less than 50% in approximately 56% of the patients, whilst 35% of the patients suffered a reduction greater than 75% (Hausman-Kedem, Menascu e Kramer, 2018). A study by Press *et al.*, published in 2015, evidenced the effectiveness of cannabis extracts in the treatment of LGS. According to this study the cannabis extracts lowered seizure frequency in 88.9% of patients, even though some patients experienced adverse effects, including seizure worsening, which limited the use of cannabis (Press, Knupp e Chapman, 2015). The administration of CBD oral solution (Epidiolex®) has also been studied for the treatment of epilepsy. GW Pharmaceuticals, the marketing authorization holder of Epidiolex®, has sponsored several placebo randomized clinical trials (RCTs) to evaluate its use in DS, LGS, and TSC patients. In DS and LGS the administration of 20 mg/kg/day was compared to placebo. In LGS a dose-finding study was also conducted by comparing the administration of 10 mg/kg/day, 20 mg/kg/day, and placebo. DS phase 3 preliminary study results suggest a reduction of 39% in the monthly convulsive seizure frequency in the group taking Epidiolex® and 13% in the group taking placebo. On the other hand, the phase 3 preliminary study results in LGS show a reduction of 44% in the monthly frequency of drop in the group treated with CBD versus 22% in the placebo group. The differences originated by the administration of CBD and placebo were noticed in the first month of therapy and continued throughout the maintenance period. In the LGS dose-ranging phase 3 study the median reduction in monthly drop seizures in the group taking Epidiolex® 20 mg/kg/day was 42%, in the group taking Epidiolex® 10 mg/kg/day was 37% and in the placebo group was 17% (O'Connell, Gloss e Devinsky, 2017). Results on the TSC study indicate that CBD reduces significantly the seizures associated with

TSC comparatively to the placebo (Thiele *et al.*, 2021). The studies performed until now suggest that Epidiolex® is effective in epileptic seizures, especially in cases of child epilepsy (O'Connell, Gloss e Devinsky, 2017). Thus, this medicine has been approved in 2018 by the FDA and in 2019 by EMA for the treatment of seizures associated with LGS and DS (FDA, 2021; EMA, 2019).

7.2. Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic inflammatory autoimmune neurological disease that affects approximately 2.5 million people around the world and causes progressive physical, psychological, and cognitive impairment, especially in young adults (Giacoppo, Bramanti e Mazzon, 2017; Gustavsen *et al.*, 2021; Rice e Cameron, 2017). Although the etiology of this disease is still not completely known, evidence suggests that MS development occurs due to a malfunction of the immune system (Giacoppo, Bramanti e Mazzon, 2017; Gustavsen *et al.*, 2021). T and B lymphocytes destroy myelin sheets and axons in the CNS, which causes the clinical symptoms of MS, such as spasticity, and muscle spasms. Spasticity is a very common and disabling symptom, affecting approximately 80% of MS patients (Giacoppo, Bramanti e Mazzon, 2017; Gustavsen *et al.*, 2021; Rice e Cameron, 2017). It has a significant impact on the life quality of these patients and may also be associated with other complications like spasms, bladder dysfunctions, pain, sleep disorders, and depression. It is the general belief that spasticity is caused by axonal deterioration or malfunction that produces a disturbance of inhibitory interneuronal spinal pathways that, in turn, leads to an intermittent or sustained involuntary activation of muscles (Giacoppo, Bramanti e Mazzon, 2017).

The oral therapies currently used to treat mild to moderate spasticity include baclofen, tizanidine, diazepam, clonazepam, gabapentin, pregabalin and botulinum toxin. However, this medication is not completely effective in the management of such complex symptoms and its use may be limited by adverse reactions. In addition, there have been a heightened number of patients that do not respond to treatment and continue to experience frequent relapsing symptoms. This has led scientists to look for other therapeutic alternatives, such as cannabis, to lighten the symptoms of MS (Giacoppo, Bramanti e Mazzon, 2017; Rice e Cameron, 2017).

Experimental models of MS display alterations in the expression of the CB1 and CB2 receptors (Cristino, Bisogno e Di Marzo, 2020). This led to research focusing on the link between these receptors and MS pathophysiology. Studies conducted in experimental models of Theiler murine encephalomyelitis virus-induced demyelinating disease, which reproduce the demyelination that happens in the brain and spinal cord of MS patients, and chronic relapsing

experimental allergic encephalomyelitis, which recreates the relapsing-remitting phenotype of MS suggest that the activation of CBRs has a beneficial effect in MS (Arévalo-Martín *et al.*, 2003; Arévalo-Martín, Molina-Holgado e Guaza, 2012; Baker *et al.*, 2000). The CB1 receptor agonists such as, Δ9-THC, WIN 55,2122, JWH-133 and methanandamide (AEA analogue) reduced tremor and spasticity, in chronic relapsing experimental allergic encephalomyelitis mice, whilst the CB1 receptor antagonist SR141716A increased these symptoms (Baker *et al.*, 2000; Fraguas-Sánchez e Torres-Suárez, 2018). Furthermore, the genetic ablation of CB1 receptors led to more severe clinical manifestations of the disease (Musella *et al.*, 2014). In mice with Theiler murine encephalomyelitis virus-induced demyelinating disease, cannabinoid agonists improved clinical scores through immunomodulatory (Arévalo-Martín *et al.*, 2003) and anti-inflammatory mechanisms (Arévalo-Martín, Molina-Holgado e Guaza, 2012). The activation of CB2 receptors suppressed the immune response in lymphocytes isolated from autoimmune encephalomyelitis mice and patients with MS (Maresz *et al.*, 2007). The impact of eCB metabolising enzymes in MS was also studied. It was found that the FAAH inhibitors CAY100400, CAY100402 and URB597, which lead to increased levels of AEA, reduced spasticity, suggesting that this enzyme might have a role in MS pathology (Pryce *et al.*, 2013). MAGL inhibitors have shown to lower neuronal excitotoxicity and avoid demyelination (Bernal-Chico *et al.*, 2015), delaying the progression of MS in experimental models (Hernández-Torres *et al.*, 2014)**.** There have also been other studies regarding the relationship between eCB metabolizing enzymes and demyelination. For instance, a study by Feliú and colleagues, in 2017, examined the role of 2-AG in demyelination in a progressive model of MS. The inhibition of MAGL in these models led to an increase of 2-AG, which, in turn, decreased the deposit of a substance that impairs axon regeneration and remyelination (Feliú *et al.*, 2017). Also, another study published in 2018 by Elliott and colleagues, described that CBD (20 mg/kg), administered via intraperitoneal, mitigated autoimmune encephalomyelitis in a mouse model of MS through the activation of different anti-inflammatory pathways (Elliott *et al.*, 2018).

After establishing the relationship between the ECS and MS as well as the therapeutic potential of cannabinoids, several clinical studies with the intent of evaluating the efficacy of cannabinoids have been performed in patients with MS and these have produced contradictory results. Killestein *et al.* reported, in a study published in 2002, that neither cannabis extracts nor Δ9-THC were efficient in ameliorating muscle spasticity. Although, the dosage of Δ9-THC used in this study (5 or 10 mg/day) might be too low (Killestein *et al.*, 2002). Furthermore, Ungerleider *et al.* had already stated, in a study published in 1988, that to achieve significant meliorations in spasticity dosages of 7.5 mg/day of Δ9-THC were necessary (Ungerleider *et al.*,

1988). A multicentered randomized, placebo-controlled trial by Zajicek *et al.*, conducted between December 2000, and October 2002, known as "Cannabinoids in MS" (CAMS) also concluded that the oral administration of both cannabis extracts and Δ9-THC at daily doses of 2.5-25 mg does not produce significant differences in spasticity symptoms relatively to the placebo group. However, researchers noticed a slight improvement of symptoms in the group treated with cannabinoids. This study used the Ashworth Scale to evaluate spasticity (Zajicek *et al.*, 2003). The Ashworth scale is a 5-point scale were a score of 0 indicates normal muscle tone and a score of 4 indicates affected limbs that are rigid in flexion/extension (Rice e Cameron, 2017). The Ashworth Scale might not be the best method to measure spasticity and, therefore, interfere with the results obtained (Zajicek *et al.*, 2003). A 12-month follow-up study by the same authors, published in 2005, shows a slight amelioration of muscle spasticity, especially in the group treated with Δ9-THC (Zajicek *et al.*, 2005). However, this data provides limited evidence for the use of cannabinoids in long-term treatments. Another study by Zajicek and colleagues, published in 2012, called "MS and Extract of Cannabis" (MUSEC), demonstrated a significant improvement in muscle rigidity in patients taking 5-25 mg/day of Δ9-THC compared to the placebo group (Zajicek *et al.*, 2012).

Sativex® (nabiximols) is a medicine approved for the treatment of the neuropathic pain and resistant spasticity symptoms in MS patients in several countries. Therefore, the efficacy of Sativex® as an add-on therapy for symptom relief in MS has been evaluated in numerous clinical trials. The first study to assess the efficacy of Sativex® was performed by Wade and co-workers in 2004. The results of this randomized, placebo-controlled, double-blind parallel group study, analyzed according to the Visual Analog Scale, demonstrated an improvement in spasticity in the group treated with Sativex® compared with placebo group (Wade *et al.*, 2004). The Visual Analog Scale is a method used to quantify spasticity, it has a score that ranges from 0 to 100, with 0 representing no spasticity and 100 maximal spasticity (Giacoppo, Bramanti e Mazzon, 2017). Although not statistically significant, patients treated with Sativex® also demonstrated improvement in mobility and bladder control. Moreover, sleep quality in MS patients taking Sativex® improved. On the other hand, no significant differences in cognition and mood were noticed between the two groups (Wade *et al.*, 2004). Consecutively, 137 of the initial 160 MS patients were monitored in an extension of the study. This extension carried out by the same authors proved the effectiveness of the long-term use of Sativex® in the patients who perceived initial benefit (Wade *et al.*, 2006). Another study performed in 2014 by Vachová and colleagues evaluated the efficacy of long-term Sativex® use on the treatment of spasticity in 121 MS patients (62 receiving Sativex®, 59 receiving placebo), that did not

respond to conventional anti-spasticity therapy. This study demonstrated that long-term treatment with Sativex® improves spasticity and is not related to cognitive impairment nor significant mood changes (Vachová *et al.*, 2013). Since the approval of Sativex® for the management of MS-related spasticity, in several European countries multiple observational post-approval studies have been conducted to monitor its use in everyday clinical practice. For instance, both the German (2014) and Italian (2015) Mobility Improvement 2 (MOVE 2) studies confirmed that Sativex® is an effective and well-tolerated option for the treatment of resistant spasticity in clinical practice (Flachenecker, Henze e Zettl, 2014; Trojano e Vila, 2015). This kind of studies, collets data in daily clinical practice complementing the results obtained with clinical trials by providing information from larger more heterogeneous populations (Giacoppo, Bramanti e Mazzon, 2017).

Several studies, regarding the efficacy of cannabinoid-based therapies in MS have been conducted over the years. Even though some of these studies have not demonstrated significant improvement in the MS symptoms, a subjective improvement is perceived by the cannabinoid-treated patients relative to the control group. Moreover, the different doses administered, the different study designs as well as the differences in the placebo response could lead to differences in the obtained results. Nonetheless, studies so far suggest that Sativex® may be beneficial in the treatment of MS, especially in spasticity relief.

7.3. Alzheimer's Disease

Alzheimer's disease (AD) is the most prevalent form of dementia (Schubert *et al.*, 2019). It affects over 50 million people worldwide, and its incidence is increasing mostly due to greater longevity. It is expected that by 2050 this number exceeds 130 million, which will cause a major socio-economic burden. AD is a neurodegenerative disease that causes a substantial decline of cognitive function, leading to severe confusion and memory loss (Hughes e Herron, 2019; Schubert *et al.*, 2019). It is characterized by the accumulation of beta amyloid peptide (Aβ) and tau protein neurofibrillary tangles in the brain. Even though the etiology of AD seems to be linked to a multitude of mechanisms, inflammation plays an important role in its pathogenesis. Familial forms of AD appear to be linked to an increased production of Aβ due to mutations in the genes coding for presenilin 1 and 2 and amyloid precursor protein (Cassano *et al.*, 2020; Hughes e Herron, 2019). The treatments currently available for AD include donepezil, rivastigmine, galantamine, among others (Cooray, Gupta e Suphioglu, 2020). However, the therapies currently available are limited, and incapable of reducing AD

progression, making the discovery of new treatments able to slow the progression of disease or prevent its onset crucial (Cassano *et al.*, 2020).

CBD is a compound known for its antioxidant, anti-inflammatory, and neuroprotective properties (Hughes e Herron, 2019). In this context, its potential effects in AD have been assessed by both *in vitro* and *in vivo* studies in models of Aβ-induced neuroinflammation. In AD, Aβ accumulates in mitochondria, leading to a reduction on the activity of the respiratory chain complexes as well as a reduction in the rate of oxygen consumption, which in turn leads to the production of free radicals and oxidative damage (Cassano *et al.*, 2012; Manczak *et al.*, 2006). Furthermore, the Wingless-Int/β-catenin pathway seems to be downregulated in AD due to the accumulation of Aβ (Vallée *et al.*, 2017), which leads to the hyperphosphorylation of tau protein and formation of neurofibrillary tangles (Esposito *et al.*, 2006). A study by Esposito *et al.* in 2006 showed that CBD reduces the hyperphosphorylation of tau protein, induced by Aβ, in PC12 neuronal cells. This effect of CBD seems to be mediated by the Wingless-Int/β-catenin pathway (Esposito *et al.*, 2006). The expression of peroxisome proliferator-activated receptor γ also seems to be altered in AD (Vallée *et al.*, 2017). Another study by Esposito *et al.* in 2011 showed that CBD lowers the markers of Aβ-induced neuroinflammation and promotes neurogenesis in Aβ-injured rat hippocampi, due to its capacity to activate the peroxisome proliferator-activated receptor γ (Esposito *et al.*, 2011). A study by Vallée *et al.* (2017) also concluded that the administration of CBD increases the Wingless-Int/β-catenin pathway, reducing the oxidative stress, and leads to the activation of the peroxisome proliferator-activated receptor γ, promoting hippocampal neurogenesis (Vallée *et al.*, 2017). A 2011 study by Martín-Moreno *et al.* also perceived the beneficial effects of CBD. The authors verified that CBD improves memory in mice injected with fibrillar Aβ, as demonstrated by the Morris water maze test (Martín-Moreno *et al.*, 2011). It is well known that hyperphosphorylation of tau protein is crucial in the pathogenesis of AD, therefore molecules that reduce these aggregates might be good candidates for the treatment of AD. To this regard, a study by Libro and colleagues (2017) demonstrated that CBD lowers the expression of the genes that code for the kinases responsible for the aberrant phosphorylation of tau, leading to a reduction of the hyperphosphorylation of tau (Libro *et al.*, 2017). Other cannabinoids have also been tested in AD models of disease. For instance, a study by Schubert *et al.* (2019) tested the effect of 11 cannabinoids in AD through a pre-clinical drug-screening platform, and most of the cannabinoids tested showed a protective effect against neurodegeneration (Schubert *et al.*, 2019).

Clinical studies regarding the use of cannabinoids in AD patients are limited. Although, some clinical trials have tested the effectiveness of Δ9-THC and nabilone in the treatment of anxiety, agitation and depression that originate from AD. In a study by van den Elsen and colleagues in 2015 Δ9-THC proved to be ineffective in the neuropsychiatric symptoms of AD (van den Elsen *et al.*, 2015), however, another study by the same author in 2017 showed some benefit on the use of Δ9-THC on balance and gait in patients with dementia (van den Elsen *et al.*, 2017). Regarding nabilone, a 2008 case report by Passmore describes that it reduces the agitation felt by a 72-year-old patient with AD (Passmore, 2008). However, further research to elucidate the therapeutic potential of cannabinoids in AD is needed.

7.4. Parkinson's Disease

Parkinson's Disease (PD) is a chronic and progressive neurodegenerative disorder that was first described by James Parkinson in 1817. In PD occurs an early death of the dopaminergic neurons in the substantia nigra pars compacta. This loss of neurons induces a deficiency in dopamine in the basal ganglia and leads to movement disorders which consist of the classic parkinsonian motor symptoms, such as bradykinesia, abnormal posture, resting tremor, and rigidity. However, PD patients can also express multiple non-motor symptoms that might precede the motor ones by more than a decade. Idiopathic PD pathogenesis is still not completely understood, although academics think that it might be multifactorial, involving environmental and genetic factors. Studies report an association between PD and head injury, lack of exercise, middle-age obesity, rural living, and herbicide/insecticide exposure, whilst tobacco smoke and coffee appear to lower risk to develop PD. From the genetic standpoint, it has been shown that mutations in the PINK1, Parkin, DJ-1, GBA, LRRK2, and ATP13A2 genes are associated with several types of parkinsonism. The pathophysiology of PD is complex involving several molecular and cellular malfunctions, such as oxidative stress, mitochondrial dysfunction, dysregulation of calcium homeostasis, misfolding and aggregation of α-synuclein, and neuroinflammation (Ferreira-Junior *et al.*, 2020a, 2020b; Patricio *et al.*, 2020). Even though PD prevalence is high no cure has been developed. The therapy currently available consists of dopamine precursor, levodopa that only alleviates the symptoms that result from dopamine deficiency (Fiani *et al.*, 2020). Levodopa is considered safe and effective in the motor symptoms of PD, however, its long-term efficacy is limited by the development of disabling motor complications. Thus, it is crucial to find more effective and tolerable treatments to retard the degradation of neurons and improve the quality of life of PD patients (Ferreira-Junior *et al.*, 2020a).

The benefits of the "Indian hemp" on parkinsonism were first noticed by Gowers in 1888 (Ferreira-Junior *et al.*, 2020b). A century later, the interest in the use of cannabis in PD has grown, mainly due to the high expression of ECS elements in the basal ganglia, which led to an increase on the investigation of the role of the ECS in movement control (Ferreira-Junior *et al.*, 2020b; Fraguas-Sánchez e Torres-Suárez, 2018). In an analysis of post-mortem brain samples from PD patients, conducted by Hurley and colleagues in 2003, a reduced expression of CB1 receptors in the anterior dorsal putamen, the caudate nucleus, and the external segment of the globus pallidus was noted. However, CB1 receptor expression remained unaltered in the anterior and posterior ventral putamen, the nucleus accumbens, and the substantia nigra. These results indicate that the expression of CB1 receptors is influenced by alterations in dopaminergic neurotransmission (Hurley, Mash e Jenner, 2003). A study by Pisani *et al.*, in 2005 examined samples of cerebrospinal fluid from PD patients at different stages of disease and demonstrated a significant rise in the AEA levels. The increased levels of AEA were independent from the disease-stage. In monkeys, this up-regulation of AEA in the cerebrospinal fluid is restored by levodopa, which suggests that the elevated levels of AEA are a compensatory mechanism for the depletion of dopamine that happens in PD (Pisani *et al.*, 2005). Higher levels of AEA have also been detected in other animal models of PD. In a study published in 2002, Gubellini and co-workers noted increased striatal levels of AEA, in rodents with 6-hydroxydopamine nigral lesions. They also noted that several rat models presented a decreased activity of FAAH and the AEA membrane transporter. However, this did not interfere with AEA binding to cannabinoid receptors. Authors also noticed that 2-AG levels remained unchanged (Gubellini *et al.*, 2002). FAAH and MAGL inhibitors have also been studied for the treatment of PD. The inhibition of FAAH prevented motor impairment in mouse models (Celorrio *et al.*, 2016; Viveros-Paredes *et al.*, 2016). However, regarding its neuroprotective effect, contradictory results have been presented. A study by Celorrio and colleagues, in 2016, stated that URB597, a FAAH inhibitor, did not reduce the dopaminergic loss in the nigrostriatal pathway (Celorrio *et al.*, 2016), whilst in another 2016 study Viveros-Paredes and colleagues reported that the chronic administration of this FAHH inhibitor lowered the death of dopaminergic neurons (Viveros-Paredes *et al.*, 2016). In 2014 Fernández-Suárez and co-workers found that in mouse models of PD the inhibition of MAGL with JZL184 (8mg/kg), led to higher levels of 2-AG, preventing motor impairment, and increasing the number of dopaminergic neurons, most likely through the activation of restorative astroglia and microglia and the release of anti-inflammatory and neuroprotective molecules. These data suggests that 2-AG might have a neuroprotective effect and that the progression of PD can be modified through the modulation of eCB levels (Fernández-Suárez *et al.*, 2014). Synthetic

cannabinoid agonists, like WIN55,212-2 (non-selective cannabinoid receptor agonist) or JWH015 (CB2 receptor agonist) also seem to be beneficial in experimental models of parkinsonism. This effect seems to depend on CB2 but not CB1 receptors (Price *et al.*, 2009). Moreover, CB2 receptors are increased in microglial cells within the striatum and substantia nigra of experimental mice models of PD and the substantia nigra of PD patients (Gómez-Gálvez *et al.*, 2016). Beyond eCBs, the effects of phytocannabinoids in PD have also been studied. For instance, in a study by Lastres-Becker *et al.* in 2005, Δ9-THC and CBD reduced the decrease in dopamine levels provoked by 6-hydroxydopamine (Lastres-Becker *et al.*, 2005) and, in another study by Garcia *et al.* in 2011, Δ9-Tetrahydrocannabivarin (Δ9-THCV) decreased the motor deficit and diminished the dopaminergic neuron loss in the substantia nigra in rodents treated with 6-hydroxydopamine (García *et al.*, 2011).

Regarding clinical trials investigating the effects of cannabinoids on PD, the results obtained have been conflicting. A 2004 study by Venderová *et al.* showed that the spontaneous use of natural cannabis produced significant ameliorations of multiple PD symptoms, such as, resting tremor, bradykinesia, and stiffness with few side effects (Venderová *et al.*, 2004). A 2014 observational study conducted by Lotan and colleagues also showed that smoked cannabis improved rigidity, tremor, and bradykinesia in PD patients (Lotan *et al.*, 2014). However, a 2004 RCT by Carroll and co-workers, concluded that the oral administration of a Δ9-THC/CBD extract produced no significant benefits on dyskinesia or other PD symptoms (Carroll *et al.*, 2004). The studies that have been carried out also focus on the possible benefits of cannabis in the treatment of PD non-motor symptoms. For instance, the above mentioned study reported a slight improvement on sleep quality in the patients that were taking cannabis compared to those who received the placebo (Carroll *et al.*, 2004). Another study, by Finseth *et al.*, published 2015, also describes the benefits of cannabis on the non-motor symptoms of PD, particularly on mood and sleep (Finseth *et al.*, 2015).

The contradictory results obtained in some of these studies might be related to variations in the amount of plant extract that is administered, the different routes of administration, among other factors. PD is a very complex disease and more double-blind, placebo controlled, RCTs with bigger samples of patients are required to enlighten the mechanisms as well as the effectiveness cannabinoids in PD.

7.5. Huntington's Disease

Huntington's disease (HD) is a progressive inherited neurodegenerative disorder characterized by neuronal loss in the striatal region (caudate and putamen), which leads to

motor and psychiatric impairment (Cristino, Bisogno e Di Marzo, 2020; Peres *et al.*, 2018). It is caused by a mutation in the huntingtin gene, located in chromosome 4 (Peres *et al.,* 2018). The diagnosis of HD is based on the motor symptoms jointly with genetic evidence, that is, a positive genetic test for the expression of the huntingtin gene or family history of HD. The pharmacological therapies currently available are still directed towards the relief of the motor symptoms that are believed to be caused by alterations in the levels of dopamine which, in turn, modulate glutamate receptor function (Peres *et al.,* 2018; Chen *et al.,* 2013). HD is believed to have two different phases, an initial one where the levels of dopamine are increased (hyperkinetic phase) and a later one where the levels of dopamine are decreased (akinetic phase) (Chen *et al.,* 2013). Therefore typical and atypical antipsychotics are usually used in the treatment of this disease, but in some cases dopaminergic agonists are needed. However, the role of dopamine in HD is still not completely understood. Concerning the cognitive deficits, none of the investigated drugs proved effectiveness. Recently, there has been a growing interest in the therapeutic potential of cannabinoids in the treatment of HD (Peres *et al.*, 2018).

Several studies have described alterations in the ECS expression in the areas involved in HD, suggesting that the ECS might play a role in disease progression. Post-mortem brain samples obtained from HD patients and experimental models of HD revealed a significant loss of CB1 receptors in basal ganglia structures, suggesting that eCB signaling is associated with HD severity and progression (Glass, Faull e Dragunow, 1993; Richfield e Herkenham, 1994). Regarding CB2 receptors, their expression was increased in post-mortem brains of HD patients as well as in experimental models and it seems to be linked to a preventive role in disease progression. On the other hand, the genetic ablation of CB2 receptors exacerbates disease in experimental models of HD (Palazuelos *et al.*, 2009). A 2004 study by Aiken and co-workers evaluated the protective effect of cannabinoids in cells expressing mutated huntingtin. The induction of huntingtin leads to rapid and extensive cell death. CBD, Δ8-THC, Δ9-THC, and CBN showed protection against cell death induced by huntingtin. However, these effects do not seem to be dependent on CB1 receptor activation since the cell line used reposted absence of CB1 receptors. The authors propose that the cannabinoids exert their protective effect through antioxidant mechanisms (Aiken, Tobin e Schweitzer, 2004). A 2007 study by Sagredo *et al.* found that in rat models treated with 3-nitropropionic acid, a compound that induces striatal damage, CBD can reverse or attenuate the damage caused by this compound. The authors propose that CBD exerts this effect through its antioxidant properties (Sagredo *et al.*, 2007). Another study published in 2011 by the same author noticed that a Sativex-like

combination of Δ9-THC and CBD had a protective effect in animal models of HD by reducing the heightened expression of the iNOS gene induced by malonate. The administration of malonate leads to striatal damage due to apoptosis and inflammatory events and, therefore, can be used as an acute model for HD (Sagredo *et al.*, 2011). A 2012 study, performed by Valdeolivas and co-workers, also stated that the administration of a Sativex-like combination in rats reduces the malonate induced alterations (Valdeolivas *et al.*, 2012).

Some clinical studies regarding the effect of cannabinoids in HD have also been conducted. A 1991 study conducted by Consroe and colleagues concluded that the administration of oral CBD did not improve cognitive, motor, or functional symptoms in HD patients (Consroe *et al.*, 1991). A more recent study published in 2016 by López-Sendón Moreno and co-workers analyzed the effect of Sativex® in HD. Despite the favorable results obtained in the preclinical trials this study failed to detect improvements in symptoms or molecular changes in biomarkers. Nonetheless, no severe adverse effects or clinical worsening was noted (López-Sendón Moreno *et al.*, 2016). Contrary to the results above, a 2018 study by Saft *et al.* reported that the administration of cannabinoid drugs to 7 HD patients (2 of which were treated with Sativex®; whilst the others received dronabinol or nabilone) displayed improvement in motor symptoms (Saft *et al.*, 2018). Also, a 2009 pilot study, performed by Curtis *et al.* determined that nabilone had a positive effect on chorea (Curtis *et al.*, 2009). Although these findings are promising, more studies are needed to establish the potential use of cannabinoids in HD.

7.6. Schizophrenia

Schizophrenia is a psychiatric chronic disease characterized by the existence of positive, negative, and cognitive symptoms (Fernández-Ruiz *et al.*, 2020; Manseau e Goff, 2015). Positive symptoms comprise hallucinations, delusions, and disorganized thinking, whilst negative symptoms include amotivation, social withdrawal, and affective flattening. Cannabis specially its main psychoactive component, Δ9-THC, is well known for its ability to cause acute psychotic symptoms and it has been proven to increase the vulnerability to develop psychotic illness (Manseau e Goff, 2015). The use of Δ9-THC has been associated with a heightened risk of developing psychosis in a dose-dependent manner, with regular and heavy users of cannabis being two and four times more susceptible to develop psychosis, respectively (Di Forti *et al.*, 2009; Marconi *et al.*, 2016). Furthermore, cannabis use seems to be associated with increased risk of developing earlier psychotic symptoms (Helle *et al.*, 2016; Kelley *et al.*, 2016; Large *et al.*, 2011). A 1987 longitudinal study by Andréasson *et al.* that included over 50,000 male

participants concluded that individuals who, by the age of 18, smoked cannabis had twice the risk of developing schizophrenia and chronical users had six times the risk when compared to non-users (Andréasson *et al.*, 1987). A review by Hasan *et al.* in 2020 also concluded that psychotic illnesses are more frequent in cannabis users than in non-users, and that any lifetime use of cannabis increases the risk of psychosis by a factor of 1.4 whilst cannabis dependence increases the risk by a factor of 3.4. An early onset of psychoses in cannabis users comparatively to non-users was also noted. Moreover, the literature also suggests that cannabis use leads to more relapses, more hospitalizations, and increases positive symptoms whilst cannabis abstinence reduces the risk of poor outcomes (Hasan *et al.*, 2020). Other studies evaluating the effects of cannabis is schizophrenia have come to the same conclusions. For instance, a cohort study by Manrique-Garcia *et al.* in 2014 showed that schizophrenic patients with a history of cannabis use had more hospital readmissions and their permanence in the hospital was longer, compared with those without a history of cannabis use (Manrique-Garcia *et al.*, 2014). A 10-year follow-up study after the first hospitalization, by Foti *et al.* in 2010, concluded that the use of cannabis after the onset of schizophrenia is associated with more severe psychotic symptoms (Foti *et al.*, 2010).

As previously mentioned, the harmful effects of cannabis in patients with schizophrenia are mainly due to the presence of the psychoactive component Δ9-THC. CBD, on the other hand, has demonstrated potential benefits in schizophrenia. In a recent RCT, published in 2018, McGuire and colleagues suggest that alongside antipsychotic therapy 6-week daily administration of 1000 mg/day of CBD reduces positive symptoms and improves functional outcomes (McGuire *et al.*, 2018). Furthermore, in a 2012 study, Leweke and colleagues compared the efficacy of CBD with a potent antipsychotic, amisulpride, in acute schizophrenia, and reported similar efficacy in amelioration of symptoms as rated by the Positive and Negative Symptom Scale (PANSS), however CBD presented superior side effects (Leweke *et al.*, 2012). While these studies were supportive of the use of CBD in schizophrenia, a 2018 trial conducted by Boggs and colleagues, were patients received 600 mg/day of CBD, did not perceive any improvement in symptoms, or in cognition compared to placebo in schizophrenic stable treated patients (Boggs *et al.*, 2018). Even though CBD and CBD-based preparations show a promising future in the treatment of schizophrenia, more studies are needed in order to establish the safety and therapeutic index of such therapeutic agents.

7.7. Major depressive disorder

Depression is one of the most frequent mental illness having a lifetime prevalence of approximately 15-20%, causing an enormous suffering. Major depressive disorder (MDD) is a

mood disorder characterized by episodes of depression that last for more than 2 weeks. It is often associated with feelings of guilt, low self-esteem, inability to experience pleasure, anxiety, disturbed sleep and appetite patterns, impairment in memory and suicidal thoughts. The first antidepressant drugs appeared in the 1950s, they were the monoamine oxidase inhibitors and the tricyclic antidepressants. However, this first generation of antidepressants, were toxic and poorly tolerated, thus, they were widely replaced by the norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors and atypical antidepressants, which have a better safety profile. The treatments currently available are generally safe and effective, however, 30% of the patients are resistant to these medicines. Moreover, these drugs have to be administered for weeks or even months before patients start to feel their effects. Therefore, there is an emergent need to develop safer, more effective, and faster acting therapies (Micale *et al.*, 2015).

The interest in the dysfunction of the ECS in depressive disorders emerged after the use of rimonabant (antagonist of the CB1 receptor) was prohibited due to several psychiatric side effects such as depression, anxiety, and suicidal thoughts (Micale *et al.*, 2015). Cannabinoids have shown a relation to both the pathogenesis and treatment of mood disorders, especially depression. This might explain why patients with depression may benefit from cannabis therapy, whilst cannabis abusers sometimes display depression (Fernández-Ruiz *et al.*, 2020).

The pharmacological modulation of the ECS has demonstrated antidepressant properties in some preclinical models of disease. For instance, a 2005 study by Hill and Gorzalka indicates that enhancement of the activity of the CBI receptor produces antidepressant effects in rats submitted to a forced swim test (Hill e Gorzalka, 2005). These results are congruent with the fact that CB1 receptors are in abundance in brain structures involved in mood control, such as the amygdala, prefrontal cortex, and hippocampus (Viveros, Marco e File, 2005). Furthermore, a 2012 study by Vinod *et al.* demonstrated that the inhibition of the eCB degrading enzyme FAAH, which leads to elevated levels of AEA, presents antidepressant effects in rat models of disease (Vinod *et al.*, 2012). On the other hand, a 2003 study by Shearman *et al.* reported that the use of AM251, a CB1 receptor inverse agonist, leads to antidepressant effects, contrasting with the data described above (Shearman *et al.*, 2003).

Regarding the use of cannabis in depression, a 2019 meta-analysis by Kosiba and co-workers suggests that the use of cannabis is frequent among depression patients, with approximately 34% of the surveyed patients reporting to use cannabis for mood enhancement

and amelioration of depressive symptoms (Kosiba, Maisto e Ditre, 2019). An observational study by Li *et al*., published in 2020, monitored cannabis self-administration in 1819 individuals, with the intention of determining the real-time effects of cannabis in depression symptoms and concluded that the majority of patients who use cannabis experience antidepressant effects (Li *et al*., 2020b). However, clinical trials with cannabinoid-based therapies in depression management are scarce and the results are conflicting. Some studies show some efficacy of cannabis-like medicines in MDD. For instance, a 2018 single double-blinded, placebo-controlled RCT conducted by Ghazizadeh-Hashemi *et al.* investigated the effect of the eCB palmitoylethanolamide in 58 patients with DSM-5 diagnosis of depression. The study had the duration of 6 weeks. All patients received citalopram and additionally, half of the patients also received palmitoylethanolamide as an add-on treatment. The results obtained showed markedly improvement of depressive symptoms in the group treated with palmitoylethanolamide compared with placebo. Although, neither one of the treatments showed differences in the number of remissions (Ghazizadeh-Hashemi *et al*., 2018). However, other studies suggest that the use of cannabis is harmful for MDD patients. For instance, a 40-year cohort study by Schoeler and colleagues, published in 2018, analyzed over 400 individuals at various points in time and concluded that cannabis use was related to an increased risk of receiving an MDD diagnosis (Schoeler *et al*., 2018). Other studies have led to similar results (Horwood *et al*., 2012; Rasic *et al*., 2013).

Evidence supporting the use of cannabis and cannabinoid-based therapies in MDD collected so far is limited and conflicting. Further studies assessing the potential of cannabinoids in MDD are required in order to understand how to target the ECS and produce beneficial effects rather than worsen the symptoms.

7.8. Anxiety disorders

Anxiety is a normal emotional response that works as an alert towards a potential threat or danger, however, when it becomes permanent and uncontrollable it originates a pathological state that negatively affects daily life (Fernández-Ruiz *et al*., 2020). It is associated with panic attacks, diminished sense of well-being and avoidance behavior, which leads to disturbed relationships, increased rates of unemployment, and elevated risk of suicide. Currently, the standard therapy in anxiety disorders are monoamine oxidase inhibitors, benzodiazepines, tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. However, most of the patients fail to achieve complete remission. For this reason, there is an ever-developing need for new pharmacologic

solutions for the treatment of anxiety disorders, which led researchers to turn to cannabinoids as a possible therapy (Wright, Di Ciano e Brands, 2020).

Various preclinical studies have examined the anxiolytic effects of CBD in rodent models using behavioral tests. The first preclinical studies investigating the possible anxiolytic effects of CBD produced mixed results. In 1990, Guimarães *et al.* demonstrated that the acute administration of CBD in rats, produces a 'bell shaped' dose-response curve, with CBD having an anxiolytic effect at low and intermediate doses (2.5, 5 and 10 mg/kg) (Guimarães *et al.*, 1990). A more recent review of the current body of literature showed that CBD has an anxiolytic effect, especially when administered in low to moderate doses (Blessing *et al.*, 2015). Furthermore, the studies show that results are variable according to the animal model used (Marinho *et al.*, 2015), and the duration of exposure (ElBatsh *et al.*, 2012). CBD has various molecular targets and, therefore, variable mechanisms of action. This compound is capable of activating the 5-HT1A receptors, which are targets of current anxiolytic medications (Wright, Di Ciano e Brands, 2020). This might be a way to understand its anxiolytic effects. For instance, a study by Campos and Guimarães in 2008 suggests that the activation of the 5-HT1A receptors present in the dorsolateral periaqueductal gray, a midbrain structure related to anxiety, by CBD might lead to anxiolytic effects (Campos e Guimarães, 2008). A study by Marinho *et al*. in 2015 also states the involvement of the 5-HT1A receptors in the anxiolytic effects of CBD (Marinho *et al.*, 2015).

Clinical trials assessing the anxiolytic effects of CBD have also been conducted and have shown promising results. The first clinical trials examining the effects of CBD in anxiety were performed in the 1980s (Wright, Di Ciano e Brands, 2020). In1982 Zuardi *et al.* showed that in healthy volunteers the anxiogenic effects of Δ9-THC were reduced by the oral administration of CBD (Zuardi *et al.*, 1982). Furthermore, a follow-up study conducted by the same team in 1993 demonstrated that the administration of CBD in healthy volunteers prior to an anxiety-inducing public speaking test had anxiolytic effects (Zuardi *et al.*, 1993). More recently neuroimaging studies have been conducted in the attempt of explaining these clinical results. These studies have demonstrated that CBD modulates neuronal activity in limbic and paralimbic areas, which participate in the regulation of emotional responses and are associated with anxiety (Crippa, *et al.*, 2004). Also, two studies conducted in healthy volunteers and individuals with Social Anxiety Disorder indicate that CBD might have anxiolytic effects (Bergamaschi *et al.*, 2011; Crippa *et al.*, 2011). Results from these studies show that that administration of a 400 mg single dose of CBD reduces significatively the symptoms of anxiety (Crippa *et al.*, 2011), and a 600 mg single dose of CBD improves cognitive impairment and

decreases speech performance discomfort compared to the placebo group (Bergamaschi *et al.*, 2011). A 2018 cohort by Linares *et al.* conducted in 57 healthy males reported that oral administration of 300 mg of CBD decreased anxiety in a simulated experimental speech test, whereas 150 and 600 mg did not produce significant effects. Moreover, anxiety levels were only reduced during the "performance phase" of the test (Linares *et al.*, 2019). The potential of CBD in anxiety has also been studied through retrospective studies. These studies allow researchers to investigate the effects of several preparations and doses in different patient populations. For instance, a retrospective case series by Elms *et al.* in 2019 concluded that the administration of CBD is apparently effective in decreasing anxiety related symptoms in Post-Traumatic Stress Disorder (Elms *et al.*, 2019). Furthermore, in a large retrospective case series at a psychiatric clinic CBD proved to be beneficial in patients with anxiety disorders (Shannon *et al.*, 2019). However, retrospective studies provide limited data due to lack of adequate controls and small sample sizes. Overall, CBD seems to be a promising treatment for anxiety-related disorders. However, the majority of studies so far have been conducted in healthy volunteers. Thus, future clinical trials are required to examine the effects of CBD on individuals with anxiety disorders.

Regarding the effects of Δ9-THC, its anxiolytic effect is dose dependent, with low doses being potentially anxiolytic and high doses being ineffective or potentially anxiogenic (Crippa *et al.*, 2009). A 2018 study by Colizzi *et al.* investigated anxiety as part of a larger crossover RCT. A dose of 10 mg of Δ9-THC was administered to 24 healthy volunteers, 12 of which were recreational users and the other 12 were nonusers of cannabis. The outcomes on psychotic and anxiety symptoms were assessed with the Positive and Negative Symptom Scale and the State-Trait Anxiety Inventory, whilst sedation and intoxication were assessed recurring to the Visual Analog Mood Scale and Analog Intoxication Scale. A significant acute increase in anxiety after the administration of Δ9-THC is perceived by the State-Trait Anxiety Inventory whereas the Visual Analog Mood Scale indicates an increase in mental but not physical sedation, which is consistent with the anxiogenic effects of Δ9-THC already known (Colizzi *et al.*, 2018).

7.9. Sleep disorders

Sleep is a vital physiological process that is extremely important in restorative functions which, in turn, are essential for normal daytime function. Multiple factors are involved in optimal sleep, such as timing, duration and efficiency (Suraev *et al.*, 2020). Sleep disorders are a heterogeneous group of pathologies that encompass sleep-related breathing disorders (e.g.

obstructive sleep apnea), insomnia, sleep-related movement disorders (e.g. REM sleep), parasomnias, and circadian rhythm sleep-wake disorders (Fernández-Ruiz *et al.*, 2020; Suraev *et al.*, 2020). Sleep disorders are associated with increased risk of depression, metabolic dysfunction, cardiovascular disease, and cognitive impairment. Various therapies can be used to treat sleep disorders, for instance, continuous positive airway pressure therapy is recommended as the first-line treatment in obstructive sleep apnea and cognitive-behavioral therapy is suggested as the first-line therapy for chronic insomnia. There are also pharmacological therapies for the treatment of insomnia that demonstrate faster improvement of symptoms. However, these medications can lead to dependence, tolerance, impairment of daytime cognitive function, and residual sleepiness (Walsh e Eastwood, 2020). *Cannabis sativa* has been used as a soporific since ancient times (Suraev *et al.*, 2020). Furthermore, it has been suggested that the ECS participates in the control of sleep. For instance, CB1 receptors are present in brain areas involved in the control of sleep. Therefore, CB1 receptor signaling might be involved in the release of sleep neurotransmitters. This evidence has led the researchers to believe that cannabinoids might be useful in the treatment of sleep disorders (Fernández-Ruiz *et al.*, 2020).

A systematic review and meta-analysis performed by Whiting *et al.* (2015) focused on two RCTs that investigated the use of cannabinoids for sleep disorders, among other illnesses (Whiting *et al.*, 2015). One of the studies was a 2010 crossover trial, by Ware *et al.* that compared the use of nabilone to the use of amitriptyline in 31 patients with chronic insomnia associated to fibromyalgia. At 2-week follow-up, nabilone demonstrated greater effect than amitriptyline in the improvement of sleep quality and produced better sleep restfulness. There were not noted any differences in wakefulness. Authors concluded that low dose nabilone might be a good alternative to amitriptyline for the treatment of sleep disorders in patients with fibromyalgia (Ware *et al.*, 2010). The other study was a pilot study conducted with 22 patients. This 2011 study by Prasad and colleagues indicated that dronabinol was superior to placebo in patients with obstructive sleep apnea. However, this study was too small to take any conclusions (Prasad, Radulovacki e Carley, 2011). Subsequently, a 2018 Phase II randomized, double-blind, placebo-controlled clinical trial conducted by Carley *et al.* strengthened the results obtained by Prasad *et al.* in 2011. This study was conducted in adult patients with moderate or severe obstructive sleep apnea. Patients were either treated with 2.5 mg/day of dronabinol, 10 mg/day of dronabinol or placebo, for up to 6 weeks. The results showed that dronabinol is safe and well-tolerated and it might be relevant in patients with obstructive sleep apnea (Carley *et al.*, 2018). A more recent systematic review performed by

Suraev *et al.* and published in 2020, summarizes the current existing evidence in the use of cannabinoids for the treatment of sleep disorders. After searching several electronic databases, the authors selected 14 preclinical and 12 clinical studies. The main finding of this review was that most of the studies had substantial risk of bias and did not have robust data in the form of RCTs. In this 2020 systematic review, Suraev and colleagues concluded that there was insufficient evidence to support the use of cannabinoid-based therapies in the treatment of sleep disorders. Nonetheless, they noted that the studies already performed provided promising preliminary evidence of the use of cannabinoids in obstructive sleep apnea, insomnia, REM sleep disorder, nightmare disorder, narcolepsy, and restless legs syndrome. Additional RCTs are required to clarify the safety and efficacy of cannabinoid therapies as well as to define the role of the ECS in sleep disorders. The currently ongoing studies regarding cannabis use in insomnia and obstructive sleep apnea are a step forward to better understand of the role of cannabinoids in the treatment of sleep disorders (Suraev *et al.*, 2020).

8. Conclusion

The diseases analyzed in this paper are mostly debilitating diseases that substantially affect the quality of life of patients. Furthermore, the therapies currently available for the treatment of such diseases are very limited and sometimes patients are refractory to them. This postulates the need for new therapies. Given the connection between the CNS and ECS, cannabinoid-based therapies have been shown to be a potential strategy in these cases.

The studies assessing the use of cannabinoids in CNS pathologies so far, have demonstrated promising results, especially for the use of CBD. However, apart from Epilepsy and MS, in which the effectiveness of cannabinoid-based therapies has clearly been proven, the remaining pathologies analyzed have very few evidence to support the use of such therapies. Furthermore, most of the studies conducted are preclinical studies. Even though these studies are useful to assess the potential of cannabinoids, preclinical models of disease might not mimic the effect of cannabinoids in the human body. Therefore, more RCTs, with bigger samples of volunteers, are required in order to establish the effectiveness of cannabinoids in these diseases as well as their therapeutic index, mechanisms of action and their interactions with other medicines.

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