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MARIANA MENDONÇA SANTOS

NOVAS TECNOLOGIAS E ESTRATÉGIAS TERAPÊUTICAS NO MANEJO DA OSTEOARTRITE: UMA REVISÃO DE PATENTES

ARACAJU-SE
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Dissertação apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Sergipe como requesito à obtenção do grau de Mestre em Ciências da Saúde.

Orientadora: Profa. Dra. Mairim Russo Serafini

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2023

DEDICATÓRIA

À minha irmã, por ser sinônimo de companheirismo, amor e dedicação.
Aos meus pais, referências de garra, determinação e coragem.

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“Somos espelho de nossas escolhas, de nossas decisões. Para vivermos algo que nunca vivemos, é necessário fazermos coisas que nunca fizemos.” A frase é bastante clichê, mas é a verdade que guia meus dias. E para chegar até aqui foi necessário mover montanhas que até então não tinha tido coragem de movimentar. Após, quase dois anos, consigo pôr fim a um ciclo que se iniciou a onze anos atrás. Com muitas dúvidas, medos e questionamentos, mas com um Deus que é bom o tempo todo e que colocou em meu caminho pessoas maravilhosas, que foram meu apoio, meu suporte, meu esteio durante todo esse tempo.

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RESUMO

Novas tecnologias e estratégias terapêuticas no manejo da osteoartrite: uma revisão de patentes. Mariana Mendonça Santos, Aracaju-SE, 2023.

A dor afeta milhões de indivíduos, contribuindo para o aumento das taxas de morbidade, mortalidade e incapacidade, em todo o mundo. A dor crônica é uma das principais razões pela qual as pessoas procuram atendimento médico, sobretudo pacientes afetados pela osteoartrite. Logo, o objetivo deste trabalho foi realizar uma revisão de patentes e prospecção de inovações tecnológicas e científicas para o manejo da sintomatologia da osteoartrite. A metodologia consistiu na busca de pedidos de patentes nas bases de dados da Worl Intellectual Property Organization e Espacenet, com uso dos descritores "nano*", "arthritis or arthrosis or osteoarthritis" e/ou códigos A61P19/02 e A61N, selecionando-os através da leitura inicial de título e resumo, e em seguida leitura completa do corpo da patente. Ao final, obteve-se 16 pedidos de patentes relacionadas a tratamentos envolvendo nanotecnologia no manejo da osteoartrite e 57 patentes direcionadas ao tratamento através de agentes físicos para esta patologia. A busca apresentou os principais métodos utilizando nanotecnologia, através das vias intra-articular, oral e tópica. Considerando que, fármacos baseados em nano sistemas demonstram inúmeras vantagens em relação aos medicamentos tradicionais de sistemas de liberação, devido a sua capacidade de transpor a barreira de fatores biológicos e físicos, destacando-se como uma opção em terapia de médio e longo prazo capazes de aliviar o processo degenerativo da osteoartrite. Uma outra perspectiva ao tratamento desta patologia são os dispositivos não farmacológicos, que atualmente possuem um déficit de informações científicas quanto ao seu conteúdo, parâmetros utilizados durante o uso e modo de entrega. Em sua maioria, estes equipamentos atuam através de agentes físicos utilizados, de modo geral por profissionais da saúde, principalmente fisioterapeutas, durante o processo de reabilitação do indivíduo acometido. Esses dispositivos foram classificados quanto ao tipo de tecnologia/terapia utilizada, tais como estimulação elétrica terapêutica, fototerapia, terapia ultrassônica, terapia eletromagnética, termoterapia e ainda a associação entre estas terapêuticas. Por fim, os dados obtidos podem auxiliar no desenvolvimento de novos protocolos, estratégias terapêuticas e tecnologias inovadoras no manejo da sintomatologia da osteoartrite, trazendo uma luz a elucidação desta patologia, que atualmente caracteriza-se como um problema de saúde pública. Logo, a possibilidade da união de abordagens terapêuticas que envolvem nanotecnologia ao uso de dispositivos modernos e inovadores para o tratamento da osteoartrite apresenta-se como uma alternativa potencial para o tratamento e cura desta doença.

Palavras-chave: Dor. Dispositivos. Nanotecnologia. Osteoartrite. Patentes. Sintomas. Sintomatologia. Tratamentos.

ABSTRACT

New technologies and therapeutic strategies in the management of osteoarthritis: a patent review. Mariana Mendonça Santos, Aracaju-SE, 2023.

Pain affects millions of individuals, contributing to the increase in morbidity, mortality and disability rates worldwide. Chronic pain is one of the main reasons why people seek medical attention, especially patients affected by osteoarthritis. Therefore, the objective of this work was to carry out a review of patents and prospecting for technological and scientific innovations for the management of osteoarthritis symptoms. The methodology consisted of searching for patent applications in the databases of the World Intellectual Property Organization and Espacenet, using the descriptors "nano*", "arthritis or arthrosis or osteoarthritis" and/or codes A61P19/02 and A61N, selecting them through the initial reading of the title and abstract, and then the complete reading of the body of the patent. In the end, 16 patent applications were obtained related to treatments involving nanotechnology in the management of osteoarthritis and 57 patents directed to the treatment through physical agents for this pathology. The search presented the main methods using nanotechnology, through intra-articular, oral and topical routes. Considering that drugs based on nanosystems demonstrate numerous advantages compared to traditional drugs with delivery systems, due to their ability to overcome the barrier of biological and physical factors, standing out as an option in medium and long-term therapy capable of alleviate the degenerative process of osteoarthritis. Another perspective for the treatment of this pathology are non-pharmacological devices, which currently have a deficit of scientific information regarding their content, parameters used during use and mode of delivery. For the most part, these devices work through physical agents used, in general, by health professionals, mainly physiotherapists, during the rehabilitation process of the affected individual. These devices were classified according to the type of technology/therapy used, such as therapeutic electrical stimulation, phototherapy, ultrasonic therapy, electromagnetic therapy, thermotherapy and also the association between these therapies. Finally, the data obtained can help in the development of new protocols, therapeutic strategies and innovative technologies in the management of osteoarthritis symptoms, bringing light to the elucidation of this pathology, which is currently characterized as a public health problem. Therefore, the possibility of combining therapeutic approaches involving nanotechnology with the use of modern and innovative devices for the treatment of osteoarthritis presents itself as a potential alternative for the treatment and cure of this disease.

Keywords: Devices. Nanotechnology. Osteoarthritis. Pain. Patents. Symptoms. Symptomatology. Treatments.

LISTA DE TABELAS

LISTA DE ILUSTRAÇÕES

LISTA DE SIGLAS E ABREVIATURAS

AA	Ácido Araquidônico
AINEs	Anti-Inflamatórios Não-Esteroidais
anti-NGF	Fator de Crescimento Anti-nervo
AVD's	Atividades de Vida Diária
CCL2	Proteína Quimioatraente de Monócitos 1
CCR2	Receptor de Quimiocina C-C tipo 2
CID-11	Classificação Internacional de Doenças
COVID-19	Coronavírus
COX-1	Ciclooxigenase-1
COX-2	Ciclooxigenase-2
CTEMs	Células-tronco Embrionárias
CTMs	Células-tronco Mesenquimais
CTPis	Células-tronco Pluripotentes Induzidas
CD	Corno Dorsal
ECS	Receptores Endocanabinóides
EPO	European Patent Office
FDA	*Food and Drug Administration*
GABA	Ácido Gama-Aminobutírico
IACSs	Injeções Intra-articulares de Corticosteroides
Igs	Imunoglobulinas
IL-1β	Interleucina 1β
IL-6	Interleucina 6
IL-8	Interleucina 8
INPI	Instituto Nacional de Propriedade Industrial
MMPs	Metaloproteinases
MOR	Receptores μ-opioides
NAPQI	N-acetil-p-benzoquinonaimina
NO	Óxido Nítrico
NOS	Óxido Nítrico Sintetase
NPs	Nanopartículas
NSP	Neurônios Sensoriais Primários
OA	Osteoartrite
OAI	*Osteoarthritis Initiative*
OARSI	*Osteoarthritis Research Society International*
OMS	Organização Mundial da Saúde
OPRM1	Gene dos Receptores μ-opioides
PEG	Polietilenoglicol
PGE2	Prostaglandina E2
PGs	Prostaglandinas
PLGA	Poli (ácido Iáctico-co-glicólico)
PVP	Polivinilpirrolidona
RVM	Medula Rostral Ventromedial
SNC	Sistema Nervoso Central

TENS	Estimulação Elétrica Nervosa Transcutânea
TNF-α	Fator de Necrose Tumoral α
US	Ultrassom Terapêutico
USPTO	United States Patent and Trademark Office
WIPO	World Intellectual Property Organization

SUMÁRIO

1 INTRODUÇÃO

A dor afeta milhões de indivíduos, contribuindo para o aumento das taxas de morbidade, mortalidade e incapacidade (ABRAMOFF et al., 2020). De acordo com a Associação Internacional para o Estudo da Dor, a dor é definida como uma experiência sensorial e emocional desagradável associada a dano tecidual real ou potencial (FILLINGIM, 2017). Dependendo da duração desse dano, a dor pode ser considerada aguda ou crônica. A dor aguda é resultado de estimulação nociva de dano tecidual e processos inflamatórios relacionados, apresentando aspectos psicofisiológico desagradável e dinâmico (PAK et al., 2018).

Neste contexto, nos casos em que a dor persiste após 3 meses, período considerado normal de cicatrização, esta passa a ser patológica e nomeada como dor crônica (COHEN; VASE; HOOTEN, 2021; TREEDE et al., 2019). A dor crônica é associada as restrições de mobilidade e atividades de vida diárias e redução da qualidade de vida, afetando mais 30% das pessoas em todo o mundo (COHEN; VASE; HOOTEN, 2021; DAHLHAMER et al., 2018). Em se tratando do Brasil, apesar de não haver muitos estudos epidemiológicos, algumas pesquisas confirmam semelhança na estatística mundial (VASCONCELOS; ARAÚJO, 2018).

A dor crônica é uma das principais razões pela qual as pessoas procuram atendimento médico, sobretudo paciente afetados pela osteoartrite (OA) (ST. SAUVER et al., 2013). A prevalência da OA eleva-se com a idade e afeta a maioria dos indivíduos com mais de 65 anos. Essa condição é caracterizada por dor nas articulações, sensibilidade, crepitação, rigidez e limitação de movimento, acometendo principalmente as articulações dos joelhos, mãos, quadris e coluna (SACITHARAN, 2019). Estando associada também com os efeitos da obesidade, o qual gera aumento do número de lesões nas articulações, a OA afeta cerca de 250 milhões de pessoas mundialmente (HUNTER; BIERMA-ZEINSTRA, 2019).

Apesar de até então os estudos científicos disponibilizados na literatura não apontarem uma cura para a OA, tratamentos não cirúrgicos são considerados os principais manejos dessa doença, neste caso, as terapias farmacológicas e não farmacológicas, a fim de haver a diminuição da sua prevalência e garantir a eficiência dos tratamentos (SKOU; ROOS, 2019). Com relação ao tratamento farmacológico, de acordo com as diretrizes do American College of Rheumatology, o paracetamol é o medicamento de primeira escolha, seguido por anti-inflamatórios não esteroidais (AINEs), tramadol ou injeções intra-articulares de corticosteroides (IACSs) ambos utilizados para alívio da dor (PERKINS; SAHY; BECKETT, 2017). Todas essas alternativas devem ser administradas diariamente, causando dor e desconforto aos pacientes. Além disso, esses medicamentos não

podem ser utilizados durante longos períodos, devido ao possível desenvolvimento de reações adversas (LAWSON et al., 2021).

Portanto, sistemas de liberação baseados em nanomaterias sendo foco de pesquisas, visto que melhoraram as características farmacológicas dos princípios ativos (BROWN; KUMAR; SHARMA, 2019). A nanotecnologia apresenta vantagens únicas para liberação de fármacos de terapêutica para OA, tais como a permissão da liberação controlada de agentes pouco solúveis em água e pequenas moléculas, proteínas ou ácidos nucleicos solúveis em água, melhoria do direcionamento, aumento da solubilidade e estabilidade, prevenção da dispersão e degradação nos fluidos corporais e extensão da circulação do fármaco e o tempo de retenção no corpo (JIN, 2020).

Outra estratégia para o alívio dos sintomas da OA é o tratamento não farmacológico. Este pode ser baseado em atividade física direcionada, suporte da equipe multidisciplinar em seus vários aspectos e terapias alternativas (HUNTER; BIERMA-ZEINSTRA, 2019). Essas terapias são usadas como complementos aos principais tratamentos da OA, com o objetivo de aumentar a eficiência dos resultados dos tratamentos. Portanto, as intervenções comumente utilizadas são baseadas em modalidades térmicas, laserterapia, ultrassom terapêutico e eletroestimulação (DANTAS; SALVINI; MCALINDON, 2021).

Portanto, há uma necessidade permanente de pesquisas clínicas de alta qualidade para garantir que os pacientes afetados pela OA recebam tratamentos seguros e eficazes. Desta forma, o desenvolvimento de novas patentes tem recebido atenção substancial, uma vez que são as fontes consideráveis e confiáveis de inovação no desenvolvimento de novos medicamentos e estratégias terapêuticas (MUCKE, 2021). Além disso, as tecnologias protegidas pelas patentes devem ser investigadas por representarem uma ferramenta fundamental para determinar a produção e disseminação do conhecimento (MEDEIROS-NEVES et al., 2020).

Dentro do exposto, esta dissertação encontra-se dividida em capítulos: I) Artigo submetido no periódico *Critical Reviews in Therapeutic Drug Carrier Systems* o qual aborda possíveis tratamentos utilizando a nanotechnologia protegidos por patentes direcionados a OA; II) Artigo a ser submetido no periódico *Journal of Science: Advanced Materials and Devices* que discute equipamentos usados em terapias não farmacológicas para a redução dos sintomas da OA.

2 REVISÃO DA LITERATURA

2.1 A dor

A dor, apesar de ser considerada um grande problema clínico, social e econômico em comunidades ao redor do mundo, pode servir como um índice da gravidade e atividade de uma condição subjacente, um indicador prognóstico e um determinante do uso de serviços de saúde (TREEDE et al., 2019). Embora a dor seja principalmente uma experiência emocional, obtendo uma correspondência variável entre ela e o dano corporal, a dor é frequentemente tratada como um processo exclusivamente sensorial, a qual reflete um dano tecidual subjacente (COHEN et al., 2021).

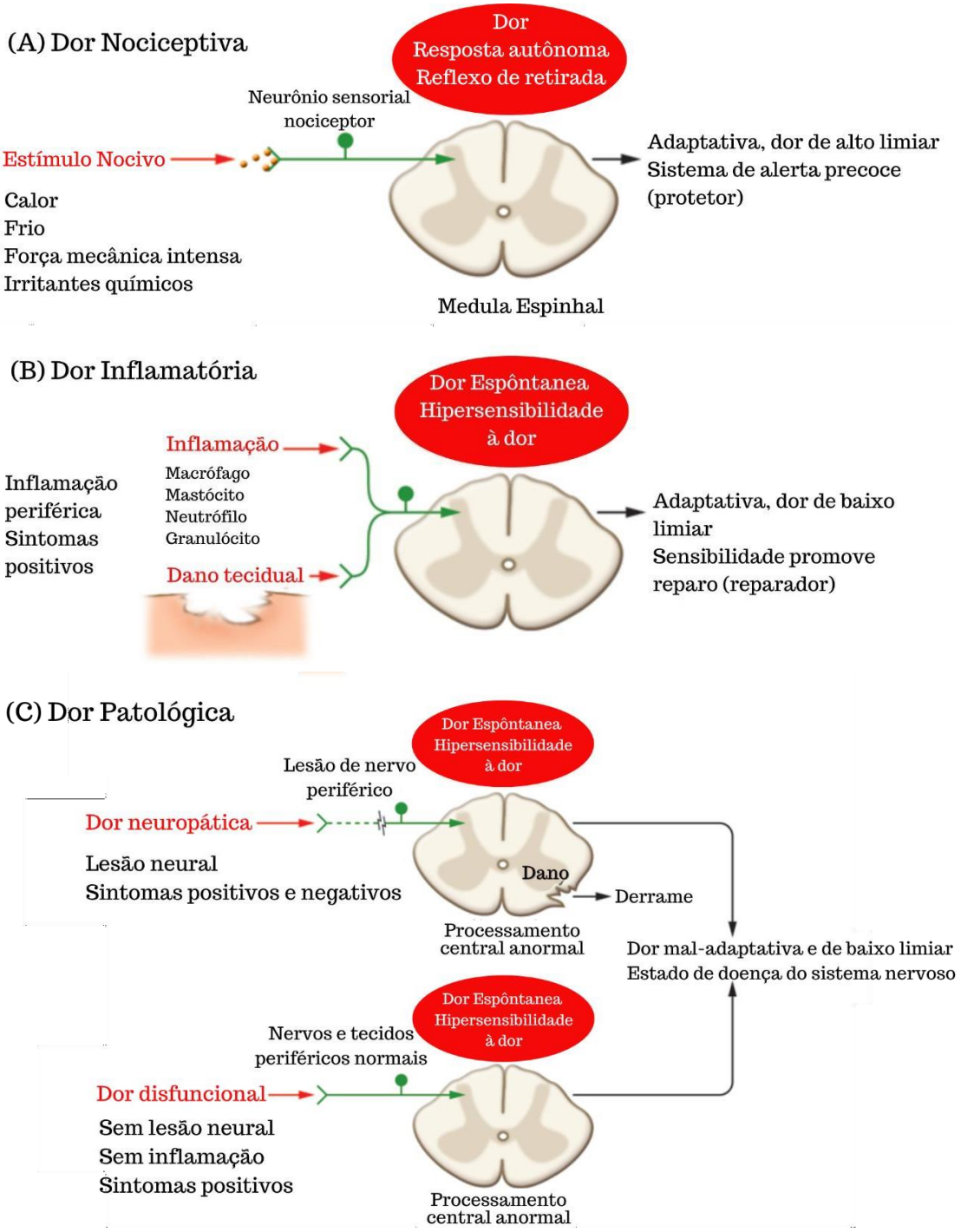
Para melhor avaliação e resposta na prática clínica, a dor é dividida em três classes: dor nociceptiva, dor inflamatória e dor patológica (PEREIRA et al., 2018). Sendo assim, a nocicepção é definida como processo neural de codificação de estímulos nocivos, determinada por um conjunto de nociceptores, que funciona como unidade primária da dor, os quais são dotados de receptores e canais iônicos que possibilitam a detecção de estímulos com potencial de causar danos (ST JOHN SMITH, 2018). Além disso, os nociceptores são compostos por duas classes principais de neurônios aferentes primários, incluindo fibras Aδ e C. As fibras Aδ são finamente mielinizadas e de tamanho médio que carregam sensações de dor aguda e localizada, enquanto as fibras C são não mielinizadas de pequeno diâmetro e de condução lenta que carregam sensação de dor difusa e queimação (GOMES; CUNHA; CUNHA, 2020; INOUE; TSUDA, 2018).

Portanto, a dor nociceptiva apresenta-se como um sinal de alerta e, quando ativado, o sistema anula a maioria das outras funções neurais (WOOLF, 2010). Em contrapartida em doenças inflamatórias, a dor é o principal sintoma clínico, causada pela sensibilização dos neurônios sensoriais primários (NSP), os quais são desencadeados por mediadores hiperalgésicos de ação direta, como as prostaglandinas (PGE2) (Figura 1a) (GOMES; CUNHA; CUNHA, 2020). Em situações de lesão e inflamação, os NSP são sensibilizados de tal forma que estímulos previamente leves ou ineficazes são capazes de ativá-los, e esta é a principal causa de hipersensibilidade à dor inflamatória (TREEDE et al., 2019).

Ademais, a dor pode se estender além de sua utilidade protetora, durando por um período de semanas a anos, muito além da resolução da lesão inicial. Neste caso, a dor é patológica e acredita-se que resulte do funcionamento anormal do sistema nervoso (Figura 1b) (TREEDE et al., 2019). Desta forma, a dor patológica é caracterizada por dor espontânea, hiperalgesia (maior

responsividade a estímulos nocivos) e alodínea (uma resposta dolorosa a estímulos normalmente inofensivos) (SUN et al., 2018).

Figura 1. Classificação da dor.



Fonte: Adaptado de Woolf et al. (2010) com permissão.

A dor nociceptiva corresponde clinicamente a dor aguda, uma vez que ambas são essenciais na defesa do corpo contra estímulos potencialmente nocivos e previne criticamente danos aos tecidos diariamente (Figura 1c) (KUNER; KUNER, 2021). A dor aguda está diretamente associada à procedimentos cirúrgicos, doenças e traumas e dura cerca de dias até

12 semanas (QASEEM et al., 2021). Estudos pré-clínicos mostram que a expressão neuronal de novos genes, que tenham como base a sensibilização e remodelação neuronal, ocorre dentro de 20 minutos após a lesão (PEREIRA et al., 2018). Portanto, a dor aguda deve ser vista como a fase de iniciação de uma extensa e persistente cascata nociceptiva e comportamental desencadeada por lesão tecidual (GILRON et al., 2019).

Entretanto, a dor aguda pode evoluir rapidamente para dor crônica, desde que a supressão das respostas à dor não tenha sido mobilizada junto com os seus processos de amplificação. Então, qualquer lesão menor pode progredir para dor crônica (PEREIRA et al., 2018). Sendo assim, indivíduos que apresentam dor crônica experimentam níveis constantes de dor ou podem apresentar episódios dolorosos que se repetem com frequência (GULSEREN et al., 2022).

Características, como composição genética, terapias medicamentosas ou outros tipos de tratamentos fisiológicos, é um fator determinante para o desenvolvimento da dor crônica (FIDLER, 2022). Ademais, a dor crônica, de acordo com a Classificação Internacional de Doenças (CID-11), é subclassificada em dor primária crônica e dor secundária crônica. A dor primária inclui aquelas condições sem uma explicação por outro diagnóstico de condição crônica, como dor crônica generalizada, cefaleia primária e síndrome do intestino irritável. Em relação a dor crônica secundária, esta é caracterizada pela identificação de uma causa distinta, como câncer, cirurgia, inflamação persistente das articulações ou vísceras, doença do sistema nervoso somatossensorial ou a OA (RAJASEKAR; KONETI, 2022).

2.2 Osteoartrite

A osteoartrite (OA) é uma das condições crônicas de saúde mais comuns, sendo uma das principais causas de incapacidade e dor crônica, representando a maior prevalência de qualquer forma de artrite (STANBOROUGH; BESTIC; PETERSON, 2022). De acordo com a Organização Mundial da Saúde (OMS), em fevereiro de 2021, cerca de 343 milhões de pessoas no mundo apresentaram sintomas de OA (WANG, Z. et al., 2022). Atualmente, existem mais de 500 milhões de pacientes com OA e no ano de 2019 essa comorbidade foi a 15ª maior causa de incapacidade entre os pacientes mais idosos (RIEWRUJA et al., 2022).

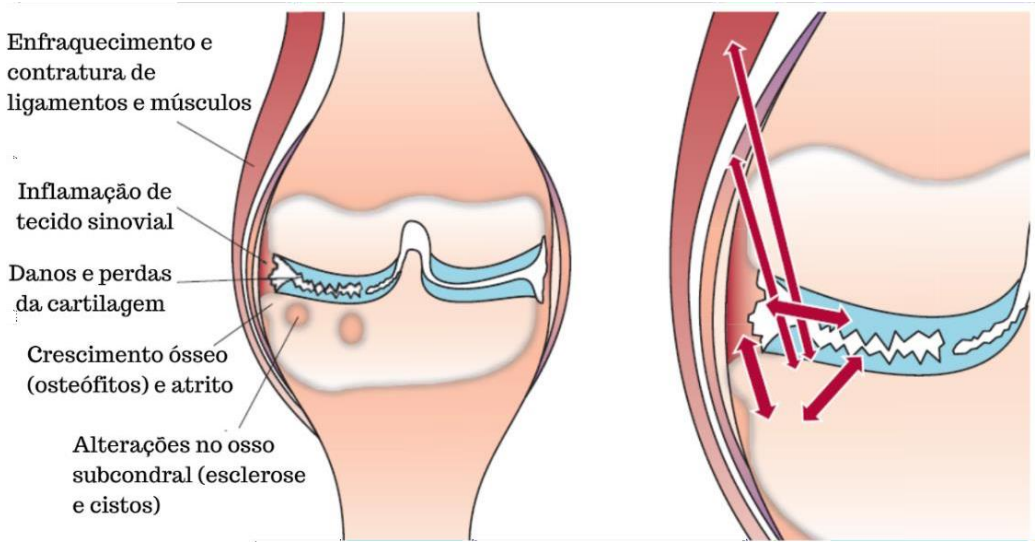
No Brasil, de acordo com a Sociedade Brasileira de Reumatologia, a OA representa cerca de 30 a 40% das consultas em ambulatórios de Reumatologia (SBR, 2022). Ademais, as principais articulações afetadas pela OA são as pertencentes aos joelhos, presente em 45% dos pacientes que possuem OA, seguido dos quadris (25%), mãos, coluna e pés (O'NEILL; MCCABE; MCBETH, 2018).

Os fatores de risco são predominantes na influência do desenvolvimento desta comorbidade degenerativa. Entre eles, destacam-se: a) idade, apesar do mecanismo de ação ser mal compreendido, entende-se que este é diretamente ligado ao enfraquecimento da musculatura com o decorrer dos anos; b) gênero, uma vez que a OA, em regiões como o quadril, joelhos e mãos, é mais prevalente em mulheres, por conta dos fatores hormonais; c) obesidade, a qual é capaz de influenciar o desenvolvimento da OA não somente de forma biomecânica, mas também por conta de efeitos dos sistemas metabólicos e inflamatórios; e d) genética, visto que muitos genes podem desenvolver papel importante no inicial da doença e, assim, fornecer alternativas para futuros tratamentos (DE KLERK et al., 2009; JOHNSON; HUNTER, 2014; SILVERWOOD et al., 2015).

Desta forma, a principal característica patológica da OA é a sensibilização da cartilagem e, posterior, dificuldade na reconstrução óssea, devido as alterações biomecânicas e bioquímicas na articulação (Figura 2) (AURICH et al., 2005; VINA; KWOH, 2018). As articulações são órgãos complexos nos quais os diferentes tecidos cooperam para o funcionamento e movimento entre os ossos do esqueleto, limitando também o grau e os eixos de movimento. Além disso, nas articulações uma fina camada de cartilagem articular cobre os ossos duros e calcificados. Sendo assim, esse tecido é rico em componentes da matriz extracelular, o que atrai moléculas de água para absorver e traduzir para os ossos as forças de carga compressiva aplicadas às articulações durante os movimentos (LORIES; LUYTEN, 2011)

À medida que a OA progride, os tecidos ósseos subcondrais, os tecidos sinoviais -tecido finos que produz líquido sinovial lubrificante-, os ligamentos articulares circundantes e os tecidos musculares sofrem alterações patológicas significativas, conforme ilustrado na Figura 2 (VINA; KWOH, 2018). Apesar da etiopatogenia da OA não ser completamente compreendida, atualmente, os estudos fisiopatológicos da OA concentram-se principalmente na apoptose de condrócitos, autofagia de senescência e lesão por estresse oxidativo, todos envolvidos em vários mediadores inflamatórios de proteases e ativação de vias de sinalização (KRISHNAN; GRODZINSKY, 2018; KULKARNI et al., 2021).

Figura 2. Desenho esquemático de uma articulação osteoartrítica.



Fonte: Adaptado de Bijlsma et al. (2011) com permissão.

Sendo assim, em pacientes acometidos pela OA, ocorre um desbalanço metabólico na cartilagem, que leva ao surgimento de sinalizadores de degradação, estimulados por cascatas de citocinas, e a produção de mediadores inflamatórios (REZENDE; CAMPOS; PAILO, 2013). Devido à ausência de vasos dentro da cartilagem, os condrócitos podem viver em um ambiente hipóxico, o qual é importante para a função e sobrevivência desses. Além disso, o desenvolvimento de canais vasculares supostamente facilita a comunicação bioquímica entre o osso e a cartilagem, iniciando um ciclo vicioso de degradação da cartilagem (JANG; LEE; JU, 2021).

No estágio inicial, como tentativa de efetuar um reparo, aglomerados de condrócitos se formam nas áreas danificadas e a concentração de fatores de crescimento na matriz intensifica (BIJLSMA; BERENBAUM; LAFEBER, 2011). Os condrócitos e as células sinoviais, produzem níveis aumentados de citocinas inflamatórias, como a interleucina 1β (IL-1β) e o fator de necrose tumoral α (TNF-α) (SAKKAS; PLATSOUCAS, 2002). Estas, por sua vez, diminuem a síntese de colágeno e aumentam mediadores catabólicos, como metaloproteinases (MMPs) e outras substâncias inflamatórias, como interleucina 8 (IL-8), interleucina 6 (IL-6), prostaglandina E2 (PGE2) e óxido nítrico (NO) (VIANNA et al., 2022).

Além disso, o estresse mecânico, tanto por compressão estática quanto por dinâmica, amplifica a produção de NO pelos condrócitos, assim como a expressão de óxido nítrico sintetase (NOS) (VIANNA et al., 2022). Os agentes oxidantes levam à apoptose dos condrócitos, que influencia nos processos catabólicos e de degeneração da matriz. Esse processo é o principal causador dos eventos patogênicos característicos do condrócitos osteoartríticos, a senescência prematura, a qual categoriza a OA como uma doença do

envelhecimento prematuro da articulação (LOESER, 2009). Todavia, estudos demonstram que a maioria dos pacientes com OA apresentam inflamação sinovial, característica principal da sinovite. Esse processo que ocorre nos estágios iniciais da OA, a sinovite geralmente é encontrada próxima a áreas com osso e cartilagem patologicamente danificados e pode ser o motivo da aceleração da destruição articular, uma vez que libera proteinases e citocinas (KRASNOKUTSKY et al., 2008).

Dessa maneira, a OA pode ser classifica de acordo com a sua etiologia em OA idiopática ou primária e secundária. Esta última é causada por condições predisponentes bem reconhecidas, que incluem anormalidades anatômicas, trauma e distúrbios inflamatórios e metabólicos (ABRAMOFF et al., 2020). A participação da hereditariedade é importante na OA secundária, principalmente em certas apresentações clínicas, como os nódulos dos dedos das mãos, chamados de nódulos de Heberden (na junta da ponta dos dedos) ou Bouchard (na junta do meio dos dedos) (SBR, 2022).

No entanto, a OA idiopática geralmente é localizada, podendo ser generalizada se a OA envolver três ou mais locais articulares (LESPASIO et al., 2017). Além disso, esta condição é caracterizada pela degeneração da cartilagem articular hialina, que leva à exposição do osso subcondral, o que contribui para a progressão da comorbidade (KWAK; JEON, 2021; LI, G. et al., 2013). A OA idiopática é amplamente desenvolvida em articulações previamente não danificadas e na ausência de um evento aparentemente desencadeante (HERRERO-BEAUMONT et al., 2009).

Desse modo, o diagnóstico precoce da OA permanece desafiador, uma vez que as alterações das cartilagens envolvidas em estágios iniciais podem não causar dor, devida à natureza aneural do tecido. Assim, os pacientes podem permanecer assintomáticos até que ocorram estágios mais avançados da doença, com danos articulares significativos e irreparáveis (BIJLSMA; BERENBAUM; LAFEBER, 2011). Nesse contexto, a alternativa escolhida é o manejo dos sintomas da OA, através de intervenções terapêuticas.

2.3 Manejo dos sintomas da OA

A dor é o sintoma predominante da OA e é o que geralmente leva os afetados a procurar atendimento médico, ainda assim a OA não tem cura (O'NEILL; FELSON, 2018). Portanto, torna-se necessário um plano abrangente de tratamento para a diminuição dos sintomas, principalmente a dor crônica, de forma individual e exclusiva para cada paciente. Os tratamentos, na sua maioria, são baseados na aplicação apropriada de terapias físicas, psicológicas ou farmacológicas (KOLASINSKI et al., 2020). A escolha da abordagem depende

diretamente do grau e do tipo de OA que o paciente é acometido. Em casos iniciais, uma única intervenção pode ser adequada para o controle dos sintomas. Entretanto, quando o paciente já se encontra em nível avançado de degeneração da cartilagem, intervenções múltiplas podem ser usadas em sequência ou combinadas entre si (MURPHY et al., 2010).

A presença de condições médicas também é um fator predominante na escolha do tratamento dos pacientes com OA, tais como hipertensão, doença cardiovascular, insuficiência cardíaca e doença renal crônica (CHOU et al., 2017a). Essas doenças podem ter impacto no risco de efeitos colaterais de alguns agentes farmacológicos assim como o tratamento físico e abordagens psicológicas (DOBSON et al., 2017). Além disso, os pacientes podem apresentar adicionalmente uma variedade de sintomas como resultado da dor e limitações funcionais da OA.

Portanto, é comum em pacientes com OA a necessidade de medidas destinadas a melhoria do humor, redução do estresse, tratamento da insônia, controle do peso e evolução da aptidão física para posterior reestabelecimento do bem-estar geral do paciente (HUNTER; BIERMA-ZEINSTRA, 2019b). Para isso, na atualidade, as intervenções que provam ser benéficas no manejo da dor crônica podem ser úteis na OA, mesmo quando os dados específicos dos pacientes são limitados (KATZ; ARANT; LOESER, 2021). Sendo assim, as opções de tratamento são geralmente classificadas como farmacológicas e não farmacológicas, as quais são classificadas complementares e alternativas (TARUC-UY; LYNCH, 2013).

2.3.1 Tratamentos Farmacológicos

2.3.1.1 Anti-inflamatórios Não-esteroidais

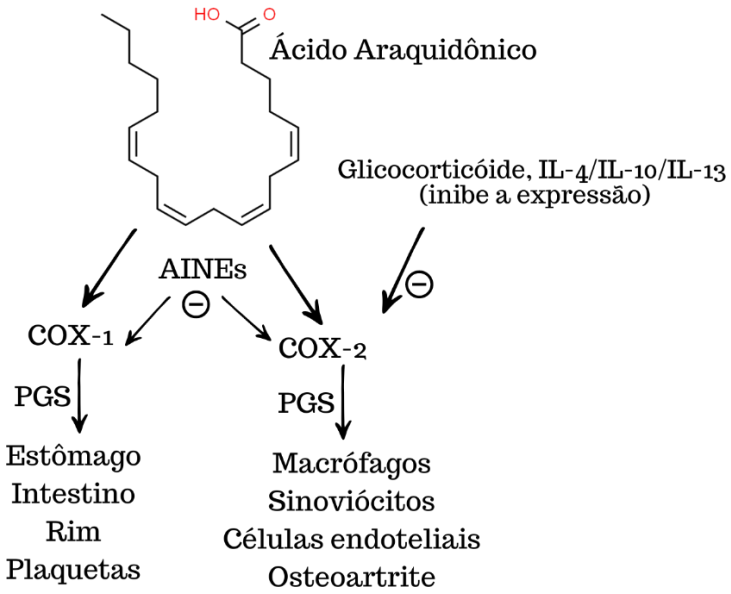
A classe de fármacos chamada de anti-inflamatórios não-esteroidais (AINEs) é a primeira linha do tratamento farmacológico para a OA, uma vez que ela consegue o alívio da dor e a diminuição da inflamação tanto na dor aguda, quanto na dor crônica (GUPTA; BAH, 2016; KATZ; ARANT; LOESER, 2021). AINEs orais são os mais comumente utilizados na área farmacêutica para o manejo da dor, sendo recomendado pela maioria das diretrizes de prática clínica como tratamento alternativo à falta de resultados satisfatórios quando os pacientes são submetidos aos exercícios, perda de peso e autocontrole (DELL'ISOLA et al., 2022).

Para pacientes que são acometidos por OA de joelho e quadril, os AINEs tópicos são recomendados devido à sua baixa exposição sistêmica, uma vez que os AINEs, quando utilizados por via oral e por períodos de tempo prolongado, apresentam muitos efeitos adversos, como distúrbios gastrointestinais (nauseas, vômitos, ulcerações, hemorragias), reações cutâneas, efeitos cardiovasculares, entre outros (BANNURU et al., 2015). Assim, apesar do seu

eficaz alívio da dor, os AINEs, quando usados por longos períodos, podem ser uma das principais causas de morbidade relacionada a medicamentos (WEHLING, 2014). Portanto, a duração do tratamento com AINEs deve ser restringida de sete a dez dias, levando em consideração o tempo necessário para atingir os efeitos analgésicos e anti-inflamatórios (MAGNI et al., 2021).

Os AINEs demonstram funcionar tanto de maneira periférica quanto central na nocicepção. Portanto, essa classe, na via ascendente da dor, atua nos nociceptores periféricos bloqueando as enzimas ciclooxigenases 1 e 2 (COX-1 e COX-2), as quais inibem a conversão do ácido araquidônico (AA) em prostaglandinas (PGs), protaciclinas e tromboxano, promovendo a sensibilização dos receptores da dor em resposta à lesão (GUPTA; BAH, 2016). Quando de maneira central, os AINEs promovem a inibição da produção de PGE2 via COX-2 no corno dorsal espinhal. No cérebro, os AINEs ativam regiões medulares e corticais envolvidas na cascata inibitória descendente da dor, levando à sensibilização central e menor limiar de dor no tecido não lesionado circundante, assim como mostra a Figura 3 (STASIOWSKA et al., 2015).

Figura 3. Mecanismo de ação analgésico dos AINEs.



Fonte: Gupta e Bah (2016). Elaborado pelo autor.

Portanto, os efeitos farmacológicos dos AINEs ocorrem devido ao bloqueio da COX e consequente redução das sínteses das PGs, o que leva à diminuição da inflamação, dor e febre. Além da vasodilatação das PGs, que reduzem indiretamente o edema, este mecanismo também explica o efeito analgésico dos AINEs (BACCHI et al., 2012). Entretanto, quando vinculados com a OA, os AINEs podem interagir e resultar em mais do que um risco associado. Estudos indicam que o uso de AINEs medeia em até 40% da associação entre OA e doenças cardiovasculares (ATIQUZZAMAN et al., 2019). Portanto, em casos em que o resultado

esperado pela terapia baseada em AINEs, não ocorra, deve ser realizada a troca por outro agente farmacológico (KOLASINSKI et al., 2020). Nesse contexto, as injeções IACSs passam a ser uma opção.

2.3.1.2 Analgésicos

2.3.1.2.1 Paracetamol

O uso dos analgésicos é comum na vida dos pacientes com OA, estando presente, aproximadamente, em 64% da rotina desses indivíduos. Além disso, pessoas com OA têm diferentes padrões de analgésicos para o uso, os quais incluem também para a mudança de classe de analgésico alternativos, assim como, a adição de outro analgésico ou a descontinuação desse medicamento (TAQI; GRAN; KNAGGS, 2021). Essa classe também pode ser classificada de forma comparativa com base na eficácia analgésica, perfil farmacocinético, efeitos colaterais mais comuns e seu mecanismo de ação (RAFFA, 2003).

Um exemplo de analgésico muito utilizado é o paracetamol, uma vez que apresenta efeito equivalente aos AINEs, apesar de não ser classificado como tal. Atualmente, este medicamento é considerado como terapia de primeira linha, por conta do seu perfil de segurança razoável (STEWART et al., 2018). Entre os participantes da *Osteoarthritis Initiative* (OAI), nos Estados Unidos, mais de 80% relataram o uso desse medicamento para dor no joelho nos últimos 12 meses (CONAGHAN et al., 2019). No estudo observacional, realizado por Conaghan e colaboradores (2015), mostrou que após duas semanas de tratamento com paracetamol, mais da metade dos pacientes, presentes no estudo com OA de joelho, relataram alívio da dor em níveis moderados e intensos (CONAGHAN et al., 2015).

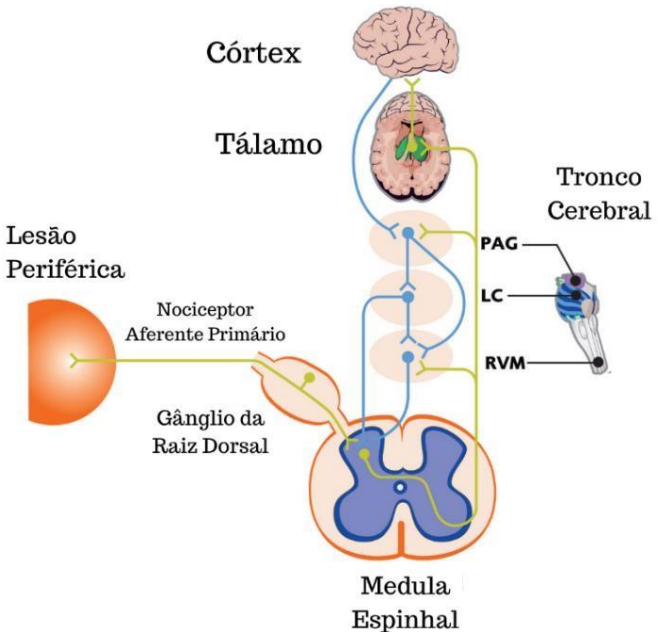
Apesar das vantagens do paracetamol, os seus efeitos adversos dependem, na sua maioria, das doses terapêuticas, assim como se consumidos em excesso nas doses recomendadas. Em alguns casos, a toxicidade pode gerar comprometimento ao fígado, assim como toxicidade gastrointestinal, cardiovascular e renal (CONAGHAN et al., 2019; GONÇALVES et al., 2022; YOON et al., 2016). Desta forma, de acordo com as diretrizes da Osteoarthritis Research Society International (OARSI), opta-se o uso do paracetamol em pacientes com OA que não têm comorbidade (MCALINDON et al., 2014). Além disso, o paracetamol fornece apenas analgesia mínima de curto prazo, mesmo em relação a placebos (LEOPOLDINO et al., 2019).

A glucuronidação e a sulfatação são as principais vias metabólicas para o metabolismo do paracetamol em dosagens usuais em adultos saudáveis. Essas vias ficam saturadas após uma

overdose de paracetamol, o que causa uma mudança para a criação do metabólito tóxico, o N-acetil-p-benzoquinonaimina (NAPQI). O NAPQI se liga à glutationa e quando esta é esgotada, o NAPQI se acumula, liga-se às células hepáticas e causa necrose hepática (LARSON, 2007; LEOPOLDINO et al., 2019; O'NEIL; HANLON; MARCUM, 2012).

Segundo Klinger-Gratz e colaboradores (2018) a perda da atividade do receptor canabinóide CB1 atenua a analgesia mediada pelo paracetamol em roedores. Ademais, o neurotransmissor lipídico anandamida é o agonista endógeno primário do receptor CB1, o qual pode promover ativação indireta dos receptores CB1, bloqueando a recaptação de anandamida. Embora os receptores CB1 sejam altamente expressos em muitas estruturas do Sistema Nervoso Central (SNC), acredita-se que a Medula Rostral Ventromedial (RVM) seja um importante local de ação do paracetamol (KERCKHOVE et al., 2014). A ativação de receptores CB1 em terminais de neurônios tonicamente ativos que liberam ácido gama-aminobutírico (GABA) que se projetam para o RVM a partir de estruturas a montante. Portanto, a diminuição resultante na liberação de GABA desses neurônios promoveria a atividade das fibras serotoninérgicas antinociceptivas, que se projetam do RVM para o corno dorsal da medula espinhal e produziriam analgesia (Figura 4) (D'ARCY et al., 2021; KLINGER-GRATZ et al., 2018; KNOOP et al., 2017).

Figura 4. Visão geral básica da sinalização nociceptiva.



Fonte: Adaptado de D'Arcy et al. (2021) com permissão.

Desta forma, devido à dificuldade em gerenciar eficazmente a dor relacionada à OA e sua capacidade de se manifestar em várias articulações, há a necessidade de novas opções de

tratamento, assim como várias novas terapias sistêmicas estão em vários estágios de desenvolvimento (CAO et al., 2020).

2.3.1.2.1 Opioides

Devido ao impacto esmagador da dor na OA e aos poucos analgésicos disponíveis no mercado que são eficazes e à medida que os tempos de espera para tratamentos cirúrgicos continuam aumentando após a pandemia do novo coronavírus (COVID-19), a prescrição de opioides tem sido cada vez mais comum, principalmente em mulheres (FARROW et al., 2021). Mais de 62% dessa classe, que apresenta OA, está em tratamento com opioides (JANI et al., 2020).

Além disso, os opioides são indicados para aqueles pacientes que não respondem a terapia com paracetamol ou AINEs e não toleram os efeitos adversos desses agentes (O'NEIL; HANLON; MARCUM, 2012). A seleção dos opioides, principalmente em pacientes idosos com dor crônica, ocorre com base em fatores, como a intensidade da dor, alterações relacionadas à idade, presença ou não de comorbidades, assim como as propriedades farmacocinéticas e farmacodinâmicas (HILMER; GNJIDIC; ABERNETHY, 2012).

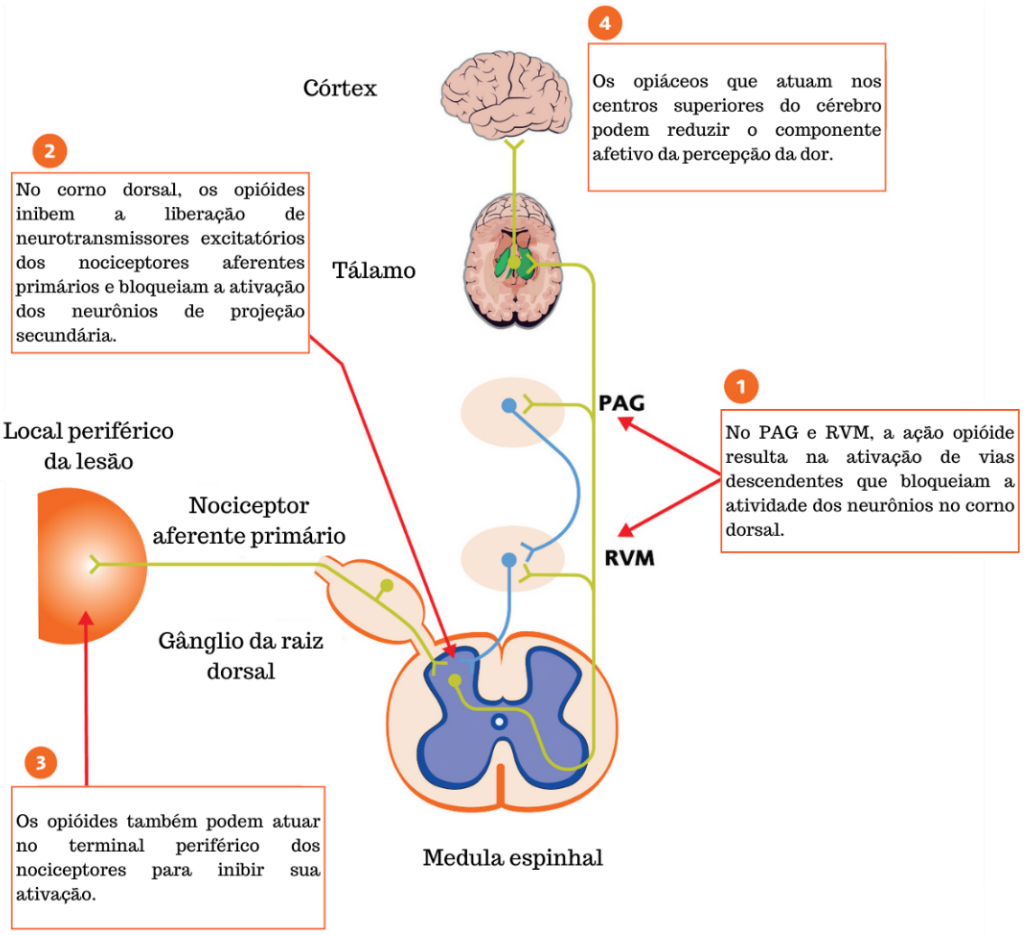
Assim como o paracetamol, os opioides não conseguem manter a eficácia por longos períodos, estando relacionados também a um risco muito maior de efeitos adversos, como a queda, que podem ser fatais em idosos (BLOCK; CHERNY, 2021). Efeitos adversos, como sonolência, sedação, náusea, vômito, tontura, boca seca, prurido e constipação, também são observados (D'ARCY et al., 2021). Portanto, após a falha dos tratamentos de primeira linha, a terapia com opioides não deve durar mais de 3 meses e as doses não devem exceder 150mg/dia. Além disso, os pacientes, quando começam o tratamento, devem ser informados dos benefícios e riscos desses medicamentos (RUIZ et al., 2018).

Evidências científicas mostram que nas décadas de 1980 e 1990, os pesquisadores demonstraram a existência de receptores opioides, não apenas no SNC, mas também em tecidos periféricos, como a cápsula articular (RICHARDS et al., 2016). Sendo assim, os efeitos dos opioides, como a morfina, são imediatos e mediados por receptores μ-opioides (MOR) acoplados à proteína G. O MOR, juntamente com outros receptores opioides, δ e κ, estão localizados no corno dorsal (DH) da medula espinhal e em outras regiões cerebrais, que apresentam resposta à dor (COLVIN; BULL; HALES, 2019; GONÇALVES et al., 2022).

Os opioides também atuam diretamente no RVM, ativando a inibição descendente, assim como visto na Figura 5 (D'ARCY et al., 2021). Por meio das ações no MOR, os ligantes opioides produzem analgesia potente e de curta duração. Entretanto, o uso repetido e

prolongado dessa classe altera a função do MOR. Segundo Viet e colaboradores (2017), o uso estendido de opioides em uma população mista de pacientes com dor crônica foi associado a maior metilação do gene MOR (OPRM1), contribuindo para a perda da analgesia mediado por opioides, assim como o aparecimento de tolerância (COLVIN; BULL; HALES, 2019; VIET et al., 2017).

Figura 5. Mecanismo de ação analgésico dos opioides.



Fonte: Adaptado de D'Arcy et al. (2021) com permissão.

O tramadol é o principal agonista opiáceo prescrito para pacientes com OA. Apesar de ser um opiáceo sintético fraco, é comumente utilizado no alívio da dor e disponível em mais de 100 países, levando ao aumento mundial do seu uso (WEI et al., 2020). Acredita-se que o tramadol induz seus efeitos anestésicos através da inibição das vias de recaptação dos neurotransmissores de noradrenalina e serotonina, além dos receptores opioides. Esse medicamento apresenta baixo potencial de abuso e perfil favorável de efeitos colaterais, justificado por sua baixa incidência de depressão respiratório, constipação e sedação (BLOCK; CHERNY, 2021; DRIESMAN et al., 2019).

2.3.1.3 Injeções intra-articulares de corticosteróides

O ensaio piloto baseado na injeção IACSs foi iniciado por White e Norton, no ano de 1958. Atualmente, esse tratamento é realizado por reumatologistas, cirurgiões ortopédicos e médicos de cuidados primários em um ambiente ambulatorial (RICHARDS et al., 2016). De acordo com a *Osteoarthritis Research Society International*, as injeções IACSs são recomendadas para pacientes em níveis de dor moderada a severa, acometidos OA multiarticular, apresentando ou não outras comorbidades, e que não obtiveram resposta satisfatória no tratamento com AINEs (MARTIN; BROWNE, 2019).

Entretanto, assim como os AINEs, as injeções IACSs apresentam benefício de curto prazo e contraindicações em casos de infecção ativa superficial da pele ou tecidos moles, suspeita de infecção articular, coagulopatia instável e pele rompida no local que a injeção seria administrada (KOMPEL et al., 2019). Ademais, as injeções de corticosteróides são recomendadas para administração uma vez a cada três meses, por um máximo de dois anos devido ao seu potencial reações adversas (RICHARDS et al., 2016). Na OA de joelho, por exemplo, os efeitos benéficos dessa terapia são observados após uma semana de tratamento e pode durar de três a quatro semanas (LAW et al., 2015).

Sendo assim, o mecanismo subjacente à eficácia anti-inflamatória dos corticosteroides é multifatorial. Geralmente seu mecanismo de ação é baseado no bloqueio da opsonização do antígeno, nesse caso as células T e B, adesão de células leucocitárias e diapedese de citocinas (TNF-α e IL-6) no endotélio capilar. Além disso, há a redução dos efeitos pró-inflamatórios do AA, uma vez que os corticosteróides agem diretamente nos receptores nucleares esteroidais. Esta classe de medicamentos também atenuam os efeitos da interleucina 1 (IL-1), diminuem a liberação de leucotrienos e PGs e inibem a síntese de MMPs e imunoglobulinas (Igs) (DONOVAN et al., 2022; DOUGLAS, 2012; RICHARDS et al., 2016; TANAKA; NARAZAKI; KISHIMOTO, 2014).

O efeito colateral mais comum observado após a injeção de corticosteróides é o agravamento dos sintomas nas primeiras 24 horas, que é geralmente seguido por uma melhora após 48 horas (TESTA et al., 2021). As injeções devem ser indolores o quanto possível, em alguns casos as administrações são realizadas com a ajuda de anestésico, como lidocaína e ropivacaína, uma vez que proporcionam ação anestésica mais rápida e duradoura. Além disso, o uso de anestésico influencia no aumento do volume injetado, para melhor distribuição do corticosteróide por toda a articulação (RASTOGI et al., 2016).

Devido a relação indireta entre a duração clínica do efeito e a solubilidade do medicamento, os corticosteróides mais usados no tratamento da OA são os insolúveis, enquanto

os solúveis são mais recomendados para injeções superficiais, uma vez que são menos prováveis de causar atrofia da gordura subcutânea ou despigmentação da pele (BLANKSTEIN; LENTINE; NELMS, 2021; RASTOGI et al., 2016). Sendo assim, existem diversos corticosteróides no mercado, na atualidade. Entretanto, frequentemente as substâncias utilizadas são acetato de metilprednisolona e acetonido de triancinolona, em dose de 40 mg com o intervalo de, pelo menos, três meses entre as injeções, conforme observado na Tabela 1 (LAW et al., 2015; MARTIN; BROWNE, 2019).

Tabela 1. Variedades de corticosteróides e dosagem.

Produto	Dose	Potência Relativa	Duração da ação
Acetato de metilprednisolona	20-80 mg	5	12-35 horas
Acetonido de triancinolona	10-40 mg	5	12-35 horas
Hexacetonida de triancinolona	10-20 mg	5	12-35 horas
Acetato de dexametasona	8 mg	25	36-72 horas
Dexametasona sódica	8 mg	25	36-72 horas
Acetato de hidrocortisona	10-25 mg	1	8-12 horas
Fosfato sódico de betametasona e acetato	0,25-2mL	20	36-72 horas

Fonte: Testa et al. (2020)

Outras injeções intra-articulares também foram desenvolvidas para o manejo da dor em paciente com OA. Dentre essas, está a injeção intra-articular de ácido hialurônico, a qual, de acordo com ensaios clínicos em humanos, reduziu significativamente a dor basal, assim como melhorou a função física e rigidez articular. Os benefícios desta abordagem foram observados em 26 semanas após uma injeção única do ácido hialurônico (LEIGHTON et al., 2018). Assim como as injeções IACSs, o ácido hialurônico é sugerido em pacientes que não se adaptaram a terapia com fármacos orais. Portanto, as injeções intra-articulares de ácido hialurônico foram reconhecidas como uma abordagem segura para a OA, apresentando reações adversas, como dor e inchaço, apenas no local da injeção ou dentro da articulação (COOPER et al., 2017; O'HANLON et al., 2016).

2.3.1.4 Outros Agentes Farmacológicos

O uso de AINEs, injeções intra-articulares de corticosteróides e analgésicos foi estabelecida como estratégia primária no manejo da dor da OA, quando esta era considerada uma doença isolada, levando, apenas, à degeneração da cartilagem. Entretanto, atualmente, a dor da OA é conceituada de forma complexa fisiopatologicamente, uma vez que apresenta diversos componentes, tais como o nociceptivo, dor inflamatória, neuropática e disfuncional.

Portanto, torna-se necessário diferentes estratégias para o manejo da sintomatologia da OA (BLOCK; CHERNY, 2021; WOOLF, 2020).

Agentes neuroativos podem ser considerados alternativas, tanto para os componentes neuropáticos quanto em relação a dor crônica da OA (DIMITROULAS et al., 2014). Conforme Gao e colaboradores (2019) , inibidores de recaptação da serotonina e norepinefrina, como a duloxetina, demonstrou efeito no alívio da dor em pacientes acometidos por OA. Aprovado pela *Food and Drug Administration* (FDA) desde 2010, para dor musculoesquelética, a duloxetina pode ser utilizada para aliviar, principalmente, dores relacionadas a OA de joelho. Outros agentes, como a gabapentina, pregabalina e diversos inibidores seletivos da recaptação de serotonina e norepinefrina são usados clinicamente para o tratamento da dor crônica (BINDER; BARON, 2016).

A indústria farmacêutica tem investido recursos para a descoberta de agentes potenciais ao alívio da dor na OA, uma vez que houve o estabelecimento de novos conceitos sobre a fisiopatologia e neurobiologia da dor. Atualmente, ainda não há agentes biológicos aprovados para o uso na OA, mas o Fator de Crescimento Anti-nervo (anti-NGF) apresenta-se em desenvolvimento, principalmente para a OA de joelho (MALFAIT; MILLER; BLOCK, 2020; MILLER; BLOCK; MALFAIT, 2018).

Na década de 1990, ainda sob investigação como potencial terapêutico para neuropatias periféricas, o anti-NGF estabelecido como um agente rápido para hiperalgesia, que impedia o seu desenvolvimento posterior, assim como apresentava potencial pronociceptivo (SCHNITZER, T. J.; MARKS, 2015). Desta forma, se propôs o desenvolvimento de anticorpos neutralizantes dirigidos contra NGF, sugeridos para variadas condições dolorosas. Tanezumab e Fasinumab são exemplos desses anticorpos que apresenta haver benefício significativo para dor, em doses 5,0 mg por via subcutânea. Embora esses agentes sejam eficazes, eles podem não fornecer um beneficia exponencial em relação à terapia atual da OA, mesmo em doses mais altas (BERENBAUM et al., 2020; GONÇALVES et al., 2022; SCHNITZER, THOMAS J. et al., 2019).

Assim como os fatores de crescimento, a atenção também foi voltada para outros mediadores da inflamação, como a proteína quimioatraente de monócitos 1 (CCL2), fator principal da quimiotaxia de leucócitos por meio do seu receptor de quimiocina C-C tipo 2 (CCR2). A CCL2 encontra-se elevada no líquido sinovial e nos fibroblastos de pessoas com OA. Sendo assim, os níveis séricos desta proteína estão associados à gravidade e progressão da OA (GSCHWANDTNER; DERLER; MIDWOOD, 2019; LONGOBARDI et al., 2017). Segundo Raghu e colaboradores (2017), no modelo de desestabilização cirúrgica de OA pós-

traumática, há o aumento rápido e intenso na expressão de CCL2 dentro da articulação. Desta forma, o eixo CCL2-CCR2 pode ter efeitos diretos nos nervos sensoriais, bem como efeitos indiretos por meio de interações neuroimunes e, portanto, interromper a sinalização CCL2-CCR2 pode ter potencial analgésico na OA (RAGHU et al., 2017).

Além disso, células-tronco também são potenciais candidatos para o tratamento da OA, principalmente quanto trata-se da regeneração da cartilagem. Dentre essas, encontram-se as células-tronco embrionárias (CTEMs), células-tronco pluripotentes induzidas (CTPis) e células-tronco mesenquimais (CTMs) (KIM et al., 2019; SHARIATZADEH; SONG; WILSON, 2019). As CTEMs e CTPis possuem características pluripotentes, as quais podem se diferenciar em outros tipos de células, incluindo condrócitos. As CTMs não são tão pluripotentes quanto as CTEMs e CTPis (IIJIMA et al., 2018; WANG, A. T. et al., 2019). Entretanto, pode ser considerada a mais ideal entre os vários tipos de células-tronco para o tratamento da OA, uma vez que as CTMs expressam e secretam vários fatores de crescimento e citocinas e possuem atividade anti-inflamatória (Tabela 2). Apesar das suas vantagens, ainda existe o risco desse tipo de terapia formar teratoma e imunogenicidade (DO AMARAL et al., 2017; STOCCO et al., 2019).

Devido aos efeitos de curto prazo observados nos medicamentos tradicionais, há um alto interesse contínuo em identificar novos produtos naturais que promovam, com segurança, a saúde das articulações. Plantas medicinais que apresentam efeito anti-inflamatório são fortes candidatos para o desenvolvimento de novas formulações (KANG et al., 2019). Dentre essas, destaca-se a *Cannabis*, uma vez que atua diretamente nos receptores endocanabinóides (ECS), tornando-se um sistema analgésico natural do corpo e alvo viável para novas terapias de OA (O'BRIEN; MCDOUGALL, 2018). Nesse contexto, os produtos naturais têm uma longa tradição no tratamento da OA e continuam sendo um tópico de pesquisa de amplo interesse (WALZER; WEINMANN; TOEGEL, 2015).

Tabela 2. Resumo das vantagens e desvantagens das células-tronco.

Células-Tronco	Vantagens	Desvantagens
Células-tronco embrionárias	Auto-renovação ilimitada Proliferação ilimitada Pluripotente Fornecimento ilimitado	Preocupações éticas Potencial tumorigênico Dificuldade no trabalho *in vitro* Dificuldade em controlar a diferenciação
Células-tronco pluripotentes induzidas	Origem autóloga Fontes extensas Auto-renovação ilimitada Proliferação ilimitada Pluripotente Sem problemas éticos	Segurança Potencial tumorigênico Ineficiência Instabilidade Mecanismo pouco claro Dificuldade em controlar a diferenciação
Células-tronco mesenquimais	Alto potencial condrogênico Boa capacidade de expansão Facilmente acessível Confiável para isolamento	Um número limitado de células Mais afetado pela idade do doador Dor no local doador

Fonte: Jang et al. (2021)

2.3.2 Nanotecnologia

A nanotecnologia é uma das tecnologias mais promissoras do século XXI. Segundo o *National Nanotechnology Initiative*, a nanotecnologia é uma ciência, engenharia e tecnologia reduzida em nanoescala, que permite novas aplicações em uma ampla gama de campos, desde a química, física e biologia, medicina, engenharia e eletrônica (BAYDA et al., 2020). Sendo assim, a nanotecnologia se preocupa em usar estruturas, controlando sua forma e tamanho, além de lidar com pequenos sistemas que aproveite algumas propriedades por causa da nanoescala (SAEEDI et al., 2019).

Em 1959 Richard P. Feynman introduziu, pela primeira vez, o conceito de nanotecnologia (CACCIATORE; BRANDELLI; MALHEIROS, 2021). Desde então, essa inovação alcançou diversas áreas de pesquisa e garante o avanço em muitos aspectos da vida humana, incluindo eletrônica, agricultura, transporte, indústria de alimentos e medicina. Quando aplicada ao campo da medicina, a nanotecnologia é chamada de nanomedicina e tem reformulado muitos aspectos da prática clínica e pesquisa, como a prevenção de doenças, diagnósticos e desenvolvimento de novas formulações (GÜVEN, 2021).

A aplicação da nanotecnologia na medicina tem atraído o interesse de pesquisa, principalmente, nos sistemas de liberação sustentada de medicamentos, uma vez que apresenta grande valor translacional (OROOJALIAN et al., 2020). Desta forma, os sistemas de liberação

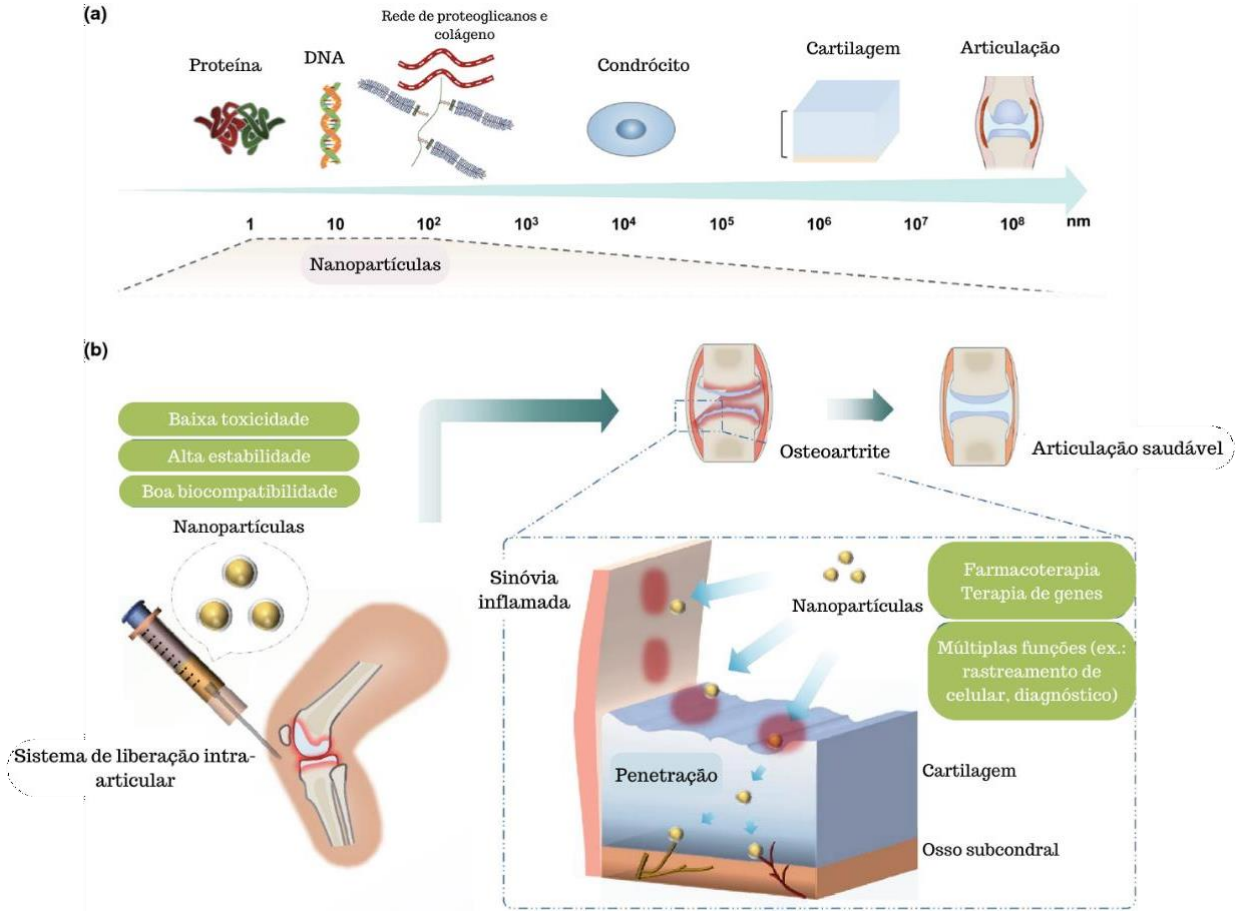
fornecem um novo método de liberação de fármacos para o tratamento de diversas doenças, visto que a manipulação em nanoescala fornece direcionamento e entrega específicos no local desejado. Nesse contexto, o desenvolvimento desses sistemas ocorre a partir de diferentes materiais, como lipídios, polímeros, metais, materiais inorgânicos e pequenas moléculas (MASOUDI ASIL et al., 2020; PATRA et al., 2018).

Para o desenvolvimento de novas formulações, a nanotecnologia está associada, principalmente, com fármacos de baixa solubilidade, por apresentarem problemas de entrega biofarmacêutica, incluindo bioacessibilidade limitada após a sua administração, menor capacidade de difusão na membrana externa, além de exigir maior quantidade de fármaco via intravenosa e apresentarem efeitos colaterais indesejados (CACCIATORE; BRANDELLI; MALHEIROS, 2021; GÜVEN, 2021; LAM et al., 2017; OROOJALIAN et al., 2020). Todavia, todas estas limitações podem ser superadas pela aplicação de sistemas de liberação nanotecnológicos (LU et al., 2016; OBEID et al., 2017).

Portanto, propriedades como tamanho, estrutura, carga superficial e pH, devem ser considerados quando em relação ao alvo de tratamento, assim como o tipo de terapia (Figura 6) (YETISGIN et al., 2020). O tamanho utilizado nas nanopartículas (), por exemplo, é fator essencial no controle da circulação e biodistribuição da formulação. Nanopartículas (NPs) menores que 10nm, podem ser facilmente filtradas através do rim, enquanto partículas maiores que 200nm podem ser depuradas por células fagocíticas no sistema reticuloendotelial (NAKAMURA et al., 2016; WU et al., 2018). Outro fator preponderante na biodistribuição é a estrutura da NPs, uma vez que dependendo desse fator, a formulação pode ser internalizada por diferentes células (YETISGIN et al., 2020).

Além disso, a carga superficial de NPs desempenha um papel importante na sua eliminação e liberação direcionada. NPs carregadas positivamente geram uma resposta imune mais alta em comparação com NPs carregadas neutras ou negativamente (WANG, C. et al., 2017). Por fim, a carga superficial também está relacionada ao pH das NPs, uma vez que estas podem ser projetadas para reconhecer e localizar os compartimentos específicos da célula. Desta forma, NPs ácidas podem ser direcionadas para endossomos ou lisossomos para liberar sua carga (HSU et al., 2017; WU et al., 2018).

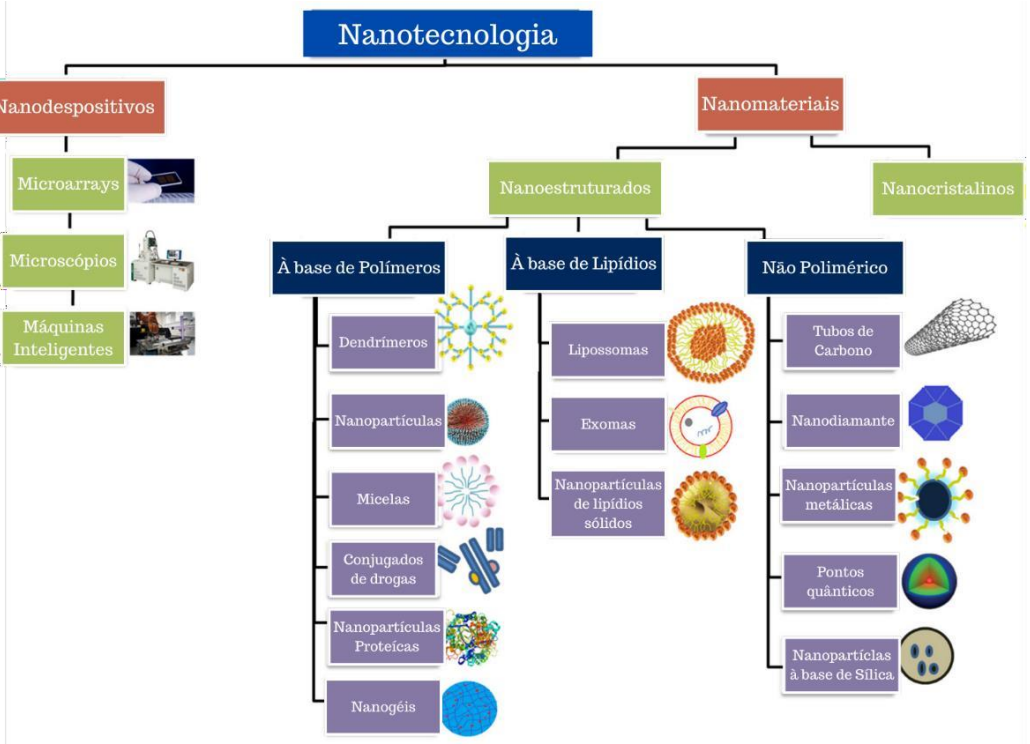
Figura 6. Propriedades e esquemas de aplicação de nanopartículas para o tratamento de doenças da cartilagem. a) Tamanho das nanopartículas em comparação com diferentes componentes em conjunto. b) Esquemas de aplicação de nanopartículas para liberação intra-articular.



Fonte: Adaptado de Li et al. (2021) com permissão.

Os sistemas nanoestruturados apresentam grande variedade quando se refere aos seus carreadores de fármacos, tais como NPs poliméricas e lipídicas, lipossomas, biomacromoléculas, dendrímeros, nanoesferas e nanotubos de carbono, trouxeram grandes avanços no campo da entrega de medicamentos, bem como em toda a área médica (Figura 7). Portanto, entre o amplo espectro de aplicações de liberação de fármacos baseadas em nanotecnologia, a ortopedia é uma das áreas de grande interesse (GÜVEN, 2021; PATRA et al., 2018; ZHANG, R. et al., 2021).

Figura 7. Elementos da nanotecnologia, que são utilizados em aplicações terapêuticas.



Fonte: Adaptado de Yetisgin et al. (2020) com permissão.

Nesse contexto, os medicamentos para a OA, apresentam rápida eliminação, direcionamento limitado da cartilagem e reações adversas graves devia a múltiplas administrações do fármaco em altas doses (MAUDENS et al., 2018). Os sistemas de liberação de medicamentos baseados em nanotecnologia vem sendo explorados para melhorar a farmacodinâmica e a farmacocinética dos medicamentos para OA, por meio de ação terapêutica direcionada e sustentada com menores efeitos adversos sistêmicos e benefícios a longo prazo (BAKHSHAYESH et al., 2020; MAUDENS et al., 2018; YAN et al., 2019).

Com o intuito de otimizar a degradação, toxicidade e propriedades mecânicas, os nanocarreadores compostos de dois ou mais componentes podem apresentar propriedades superiores comparado àqueles de apenas um princípio ativo. Com o ajuste das propriedades físico-químicas, os nanocarreadores podem ser funcionalizados para direcionamento do fármaco a alvos específicos, como cartilagem, condrócitos e outras células (LI, X. et al., 2021; SHARIFI-RAD et al., 2021). Desta forma, Zhang e colaboradores (2020) provaram a capacidade de nanovesículas compostas por exossomos derivados de CTMs em prevenir a OA, através da polarização de macrófagos sinoviais, ou seja, transformação fenotípica de macrófagos de M1 para M2.

Além disso, Maudens e colaboradores (2018) propuseram partículas de nanocristais contendo polímeros e como princípio ativo a kartogenina, a qual apresentou alta concentração

por um longo período, agindo, portanto, como um sistema de liberação controlada. A kartogenina é caracterizada como uma pequena molécula heterocíclica com a capacidade de proteção e regeneração da cartilagem. Esse estudou demonstrou maior bioatividade comparada a formulação com a kartogenina livre (GÜVEN, 2021).

Em relação a administração intra-articular, He e colaboradores (2020) desenvolveu um nanocarreador como um sistema de liberação para tal administração, fornecendo uma possível combinação de princípios ativos em apenas uma única injeção. O estudou provou eliminar problemas de toxicidade e manter a liberação sustentada dentro da articulação para o tratamento eficiente da OA.

As NPs, podem ser combinadas com veículos de liberação tópicos, para aumento da sua atividade, evitar o metabolismo hepático de primeira passagem, variações do pH gástrico e flutuações nos níveis plasmáticos, frequentemente encontrados, principalmente, quando um medicamento é administrado por via oral. Além disso, aumento da aceitação do paciente em relação à terapêutica, facilidade e conveniência de aplicação (BRENNAN-JONES et al., 2020; SINGH MALIK; MITAL; KAUR, 2016). Desta forma, Silva e colaboradores (2022) utilizaram um gel de carbopol para demonstrar o efeito do óleo de pequi (Caryocar coriaceum Wittm) em mulheres com OA de joelho.

Portanto, o óleo de pequi, quando encapsulado, presentou uma formulação estável, segura e sem irritabilidade ou toxicidade em relação ao uso tópico. Ademais, o aumento da força e funcionalidade muscular associado à redução dos sintomas do joelho e a melhora da qualidade de vida sustentam o uso desta formulação como uma possível alternativa terapêutica para o tratamento da OA ou atuar como adjuvante ao tratamento convencional, constituindo-se assim um modelo de tratamento que poderia beneficiar indivíduos com OA de joelho (SILVA et al., 2022).

Ademais, os lipossomas também podem otimizar a eficiência terapêutica e de entrega de várias formulações, estando presente na prática clínica por várias décadas (GUO et al., 2022). Chang e colaboradores (2021) desenvolveu uma formulação para o tratamento da OA, contendo ácido hialurônico, tanto para o combate das dores da OA, quanto para o seu tratamento prolongado. Sendo assim, a formulação manteve o tempo de liberação em pelo menos 168 horas sem toxicidade significativa, assim como a sua injeção intra-articular inibiu consideravelmente a inflamação da articulação do joelho durante quatro semanas.

Terapias com sistemas de liberação baseados em nanotecnologias apresentam potencial de melhorar significativamente o tratamento de diversas doenças relacionadas aos ossos, em especial a OA. Apesar deste progresso considerável, mais estudos e ensaios clínicos extensos

devem ser realizados para demonstrar sua eficácia e avaliar seus perfis de segurança a longo prazo, para que os resultados sejam traduzidos para a prática clínica (GÜVEN, 2021).

2.3.3 Terapias Não-Farmacológicas

O tratamento não-farmacológico da OA é multidisciplinar e visa a melhora funcional, mecânica e clínica dos pacientes acometidos por esta doença (HUNTER, 2019). Envolve desde programas de educação em dor, com esclarecimentos sobre a doença e orientações para a prática esportiva e atividades de vida diária (AVD's), até práticas integrativas e complementares. Dentre elas, a fisioterapia através da utilização de agentes físicos, tais como a eletro-termo-fototerapia (ABRAMOFF; CALDERA, 2020).

O agente físico tem a função de atuar na modulação da liberação de mediadores inflamatórios, regulando a dor no nível da medula espinal, alterando a condução nervosa ou aumentando os níveis de opiopeptinas. De forma indireta, diminui a dor pela redução da sensibilidade do sistema de fuso muscular, modificando o tônus vascular e a taxa de fluxo sanguíneo, reduzindo o edema ou a isquemia (SONKODI; BERKES; KOLTAI, 2020).

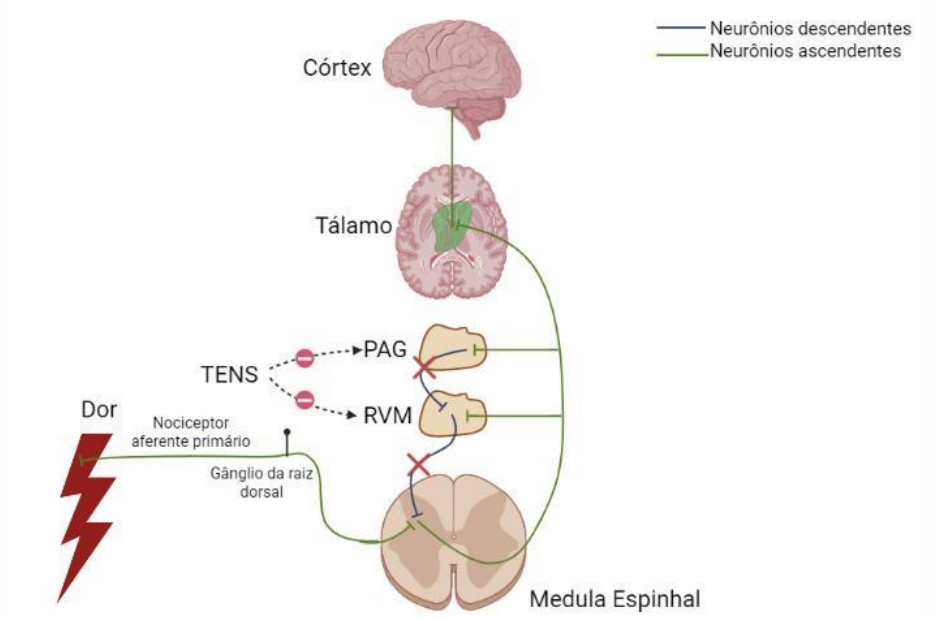
A estimulação elétrica nervosa transcutânea (TENS) é uma modalidade física amplamente utilizada no alívio da dor em pacientes com OA (KIM et al., 2019). Seu uso objetiva facilitar alterações na ação e desempenho muscular, melhorar a força da musculatura a ser aplicada, aumentando a amplitude de movimento, reduzir edemas, diminuir a atrofia muscular e o limiar de dor de modo geral na região acometida (NUSSBAUM et al., 2017). Embora vários tipos de estimulação elétrica estejam disponíveis, a TENS convencional é a mais comumente aplicada, principalmente em pacientes com OA de joelho (KIM et al., 2019).

Baseada na Teoria das Comportas, a TENS teve sua utilização iniciada como método de tratamento para dor, em 1967, onde foi combinada a geradores e condensadores eletrostáticos, resultando em um reposicionamento da eletroterapia, como alternativa terapêutica (SOUTHWELL, 2020). Em frequências e intensidades usadas clinicamente, a TENS ativa fibras aferentes de grande diâmetro. Esta entrada aferente é enviada ao sistema nervoso central para ativar os sistemas inibitórios descendentes, reduzindo a hiperalgesia. Especificamente, o bloqueio da atividade neuronal na PAG, RVM e da retransmissão na medula espinhal impedem que os estímulos dolorosos sejam conduzidos, fechando as comportas de dor e, por conseguinte, mantendo a analgesia da via. Logo, com a redução da hiperalgesia por meio de mecanismos periféricos e centrais, assim como observado na Figura 8 (VANCE et al., 2014).

Na prática clínica a TENS é fornecida, em duas modalidades, alta frequência (50 e 100 Hz) e baixa frequência (2 e 10 Hz) (NUSSBAUM et al., 2017). Entretanto, quatro tipos de

aparelhos TENS podem ser utilizados ativando uma complexa rede neuronal, no intuito de reduzir a dor local (RUTJES et al., 2009). O primeiro é de alta frequência, que se caracteriza com 40 a 150 Hz, pulsos de largura entre 50 a 100ms, intensidade moderada; o segundo é o de baixa frequência e que se constitui por ondas de 1 a 4 Hz, pulsos de largura entre 100 a 400 ms e alta intensidade; o terceiro é de frequência de explosão que possui ondas de 1 a 4 Hz, pulsos de largura entre 100 e 250 ms e alta intensidade; o quarto é de hiperestimulação contendo ondas de 1 a 4Hz, com pulsos de largura de 10 a 500 ms e alta intensidade (SOUTHWELL, 2020).

Figura 8. Mecanismo de ação da TENS.



Fonte: Vance et al. (2014). Elaborado pelo próprio autor com auxílio do *software Biorender*®.

Além disso, esta modalidade terapêutica trabalha com quatro níveis de intensidades de estímulos: subsensório, sensório, motor, nociceptivo. O nível subsensório utiliza um período da carga elétrica de amplitude insuficiente para alcançar o limiar sensório e despolarizar os axônios dos nervos periféricos ou despolarizar a membrana muscular. O nível sensório é definido como a estimulação em ou acima do limiar sensitivo e abaixo do limiar motor e é primeiramente indicado para dor aguda e subaguda, mas também tem utilidade em condições crônicas (NUSSBAUM et al., 2017). O nível motor de estimulação é usado primariamente para controle de dor não aguda. A amplitude da TENS é alta e o suficiente para produzir contração muscular visível. O nível nociceptivo é definido pela propagação pelas fibras aferentes sensoriais e proprioceptivas encobrindo o estímulo nociceptivo (SOUTHWELL, 2020).

As vantagens da TENS incluem seu fácil manejo, e possibilidade de uso isolado ou em associação a outras modalidades de tratamento, sua administração é não invasiva, não farmacológica, pode ser operado pelo próprio paciente e possui poucas restrições de uso.

Portanto, trata-se de uma modalidade terapêutica bastante abrangente e acessível (SANTANA et al., 2016).

Cherian e colaboradores (2015) em ensaio clínico randomizado e simples-cego avaliaram a eficácia do uso da TENS em pacientes com OA de joelho, os autores relataram que a TENS em comparação a terapia padrão (cinesioterapia), resultou em melhoria significativa na força muscular isocinética do quadríceps, pontuações positivas em escala de funcionalidade e de qualidade de vida, além de alívio significativo da dor nos pacientes que receberam essa modalidade terapêutica.

Ademais, apesar dos inúmeros estudos envolvendo a TENS exclusivamente ou combinada, as intensidades incluídas metodologicamente variam amplamente. Bjordal e colaboradores (2003) realizaram uma revisão sistemática sobre a TENS para a dor da OA evidenciaram que, quando administrada em intensidades e frequências adequadas a TENS produz uma redução clinicamente significativa na dor quando comparada a estudos de dosagem inadequada. Sendo assim, é de fundamental importância a correlação entre quadro clínico e a escolha das frequências apropriadas para eficácia do tratamento (MENEZES et al., 2018).

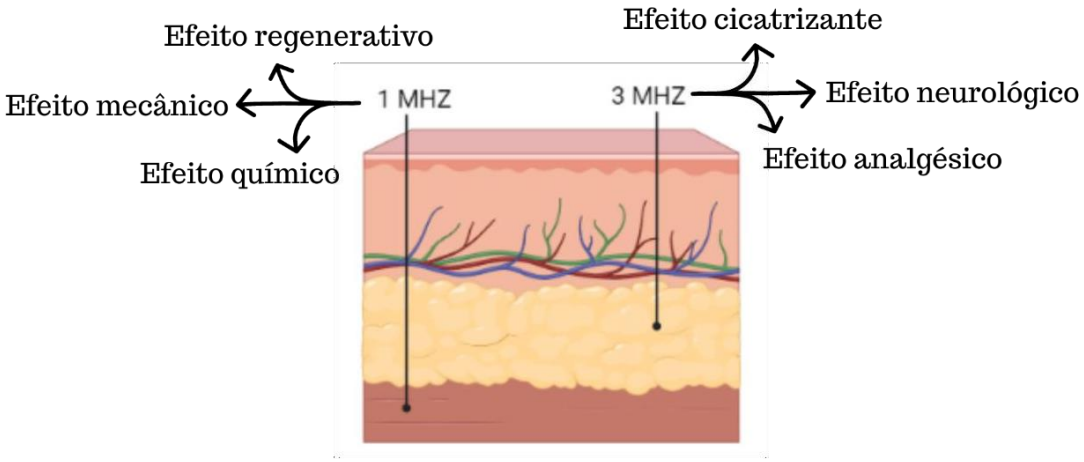
Em paralelo ao TENS, uma série de pesquisas avaliou o efeito do ultrassom terapêutico (US) de baixa intensidade na cicatrização da cartilagem usando diferentes modelos. Cook e colaboradores (2001) demonstraram o efeito terapêutico do US de baixa intensidade na cicatrização de defeitos osteocondrais de coelhos *in vivo* variando a duração de tempo diária do tratamento e o total de número de dias. Em seu estudo, aumentando o tempo de duração de cada sessão, resultou na melhora da qualidade histológica da cartilagem enquanto, o aumento do número de dias resultou em alterações menos degenerativas em comparação a um tratamento com período mais curto.

Em um outro estudo, Cook e colaboradores (2008), concluiram que o US de baixa intensidade melhorou significativamente a interface da cartilagem em cães, melhorando as características morfológicas celulares e a ligação da interface com a cartilagem local retirada. Além disso, Naito e colaboradores (2010), evidenciaram um aumento da síntese de colágeno tipo II e do RNA mensageiro de colágeno tipo II na cartilagem após o uso do US de baixa intensidade, sugerindo, assim, um mecanismo potencial de como o US induz a cicatrização cartilaginosa.

O US é um aparelho que tem o mecanismo de enviar ondas acústicas as quais são produzidas por vibrações de um cristal situado dentro de um transdutor. A frequência do transdutor pode ser de 3 MHz, mais superficial, com profundidade de 1 a 2 cm, ou 1 MHz, que atinge tecidos mais profundos de 3 a 5 cm, assim como representado na Figura 9 (JOHNS,

2002). É uma das modalidades físicas comumente usada para distúrbios musculoesqueléticos e osteocondrais, como terapêutica alternativa e não invasiva (JIANG; FANG; WU, 2019).

Figura 9. Efeito do US sob o músculo em relação a frequência das ondas.



Fonte: Johns (2002). Elaborado pelo próprio autor com auxílio do *software Biorender*®.

O uso terapêutico do US iniciou-se focado apenas nos efeitos térmicos por Wood e Loomis no final da década de 1920. Entretanto, recentemente os efeitos não térmicos têm se destacado, permitindo a expansão da variedade de aplicações terapêuticas. Sendo assim, dividido em efeitos térmicos e não térmicos. Os efeitos térmicos, resultam em aumento do fluxo sanguíneo, da atividade enzimática, condução do estímulo nervoso, limiar de dor e reduz espasmos na musculatura. A temperatura deve aumentar de 1 a 4º C (RACINAIS; COCKING; PÉRIARD, 2017). Já os não térmicos resultam da vibração das ondas acústicas, que provocam compressão e rarefação. Podendo ocasionar o aumento da deposição de colágeno, proliferação de fibroblastos, angiogênese, alterações na permeabilidade da membrana aos íons de cálcio e liberação de histamina (TENTI et al., 2013).

Entretanto, apesar de amplamente utilizado, difundido e ser alvo de estudos desde muito tempo, cientificamente sua eficácia é controversa, não possuindo uma literatura esclarecedora, segura e objetiva quantos a seu mecanismo de ação e potencial reparador. Estudos clínicos e revisões sistemáticas apontam diferentes metodologias, parâmetros e resultados, com vises clínicos e populações-teste reduzidas, permitindo assim grandes questionamentos quanto a real eficácia do uso isolado do US (CHOU et al., 2017b).

Outros agentes físicos também são utilizados no tratamento não farmacológico da OA, tais como a fototerapia, termoterapia e terapia eletromagnética. Ainda que com pouquíssima evidência, na prática clínica, as modalidades de agentes físicos são amplamente utilizadas

isoladamente ou em combinação com outros tratamentos conservadores em todas as fases da OA (RUIZ et al., 2018; TENTI et al., 2013).

2.4 Prospecção de Patentes

A demanda por serviços ortopédicos representa um desafio para o futuro, quando se refere a prestação de cuidados de saúde em todo o mundo. Consequentemente, o cenário de doenças ortopédicas tem se modificado de forma potencial, principalmente em relação as inovações tecnológicas, no que tange a elaboração de estratégias de crescimento, diferenciação e resolução de problemas (UZOIGWE; SHOAIB, 2020). Sendo assim, quando há criação de algo novo, assim como o desenvolvimento de um processo de fabricação ou aperfeiçoamento de técnicas e produtos já existente, a proteção se dá através de patentes (ARAÚJO et al., 2020).

As patentes tendem a ser protegidas através da propriedade intelectual, uma vez que se refere a um conceito de manifestação tangível ou concreta que é atribuída a proprietários específicos (CULLIFORD et al., 2015). Um dos parâmetros utilizados para avaliar o desenvolvimento de uma nação é o número de patentes concedidas (FREILICH; OUELLETTE, 2019). Portanto, uma patente deve ser um documento independente que permita ao leitor repetir os resultados apresentados. A prospecção tecnológica é fator determinante na redução de incertezas e nos processos de tomada de decisão estratégica, uma vez que 70% das informações contidas nas patentes não estão acessíveis em outros meios de informações, como artigos científicos (CERQUEIRA; SILVA; RIBEIRO, 2019; MOURA et al., 2019).

Em muitos casos, os detalhes apresentados no pedido de patente só serão publicados na própria patente, tornando-se uma fonte única de conhecimento (BRAGA et al., 2018). Além disso, as patentes também são essenciais para antecipar as tendências e sinais de mudanças mundiais. Logo, a prospecção de patentes é uma etapa fundamental do processo de inteligência competitiva, visto que é através dela é possível construir um mapa inicial de fonte de informações e conhecimentos (PARANHOS; RIBEIRO, 2018).

Bases de dados, como o Instituto Nacional da Propriedade Industrial (INPI-Brasil), *European Patent Office* (EPO-ESPACENET), *World Intellectual Property Organization* (WIPO), *United States Patent and Trademark Office* (USPTO) dispõem, asseguram e protegem as informações patenteadas. Esses bancos de dados são encontrados na internet de forma gratuita, além de contar com uma busca simples e rápida, avançada (BRAGA et al., 2018; MOURA et al., 2019). Além disso, as técnicas e métodos de prospecção tecnológicas diferem nos tipos de abordagens e nas habilidades requisitadas nas buscas (Figura 10). As buscas realizadas nas bases de dados também permitem identificar os inventores, principais

especialistas de uma determinada área, os países onde a tecnologia está protegida e, por fim, o depositante que realizou o primeiro depósito de patente (CHARREAU; CAVALLO; FORESTI, 2020).

Figura 10. Etapas da elaboração de estratégias de busca da prospecção de patentes.

Fonte: Paranhos e Ribeiro (2018). Elaborado pelo autor.

Nesse contexto, garante-se a importância da prospecção tecnológica, pois ela fornece embasamento para as tomadas de decisão formularem as estratégias de inovação e mapear os desenvolvimentos científicos e tecnológicos, visualizando as tendências de mercado (PARANHOS; RIBEIRO, 2018). O mapeamento tecnológico é ainda mais essencial no redirecionamento de medicamentos do que com novas entidades químicas, porque as reivindicações de que um desenvolvedor pode patentear para proteger a invenção são limitadas ao novo uso terapêutico e novas formulações perfeitamente adaptadas a esse novo uso e à nova população alvo (MUCKE, 2021b).

3 OBJETIVOS

3.1 Objetivo Geral

- Realizar a revisão e a prospecção de inovações tecnológicas e científicas de terapêuticas voltadas para o manejo da sintomatologia da OA.

3.2 Objetivos Específicos

- Investigar inovações terapêuticas no âmbito da nanotecnologia destinadas ao manejo da OA através da revisão de patentes;
- Identificar os principais equipamentos utilizados em terapias não-farmacológicas associadas a agentes físicos com enfoque no manejo da dor na OA.

CAPÍTULO I

The Management of Osteoarthritis Symptomatology Through Nanotechnology: A Patent Review

Artigo submetido no periódico *Critical Reviews in Therapeutic Drug Carrier Systems*

Fator de impacto de 4.889

The management of osteoarthritis symptomatology through nanotechnology: a patent review

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ABSTRACT

Osteoarthritis is greatly considered as a progressive and degenerative joint disease which is characterized by inflammation, chronic pain, and functional limitation. Due to the impacts of this disease, osteoarthritis may consume a higher amount of healthcare resources and costs as it paves way for the higher risk of hospitalization and emergency department charges. Nanotechnology has been presenting unique advantages for drug delivery of therapeutics for osteoarthritis. Nanotechnology is a branch of science which involves the manipulation and control of matter at the nanometer scale to produce new structures, materials, and devices. Moreover, the increasing development of nanotechnology in drug delivery systems has provided new ideas and methods for osteoarthritis therapy. Thus, this review aims to evaluate patents that have developed innovations, therapeutic strategies, and alternatives using nanotechnology in the osteoarthritis treatment. The results show patents deposited from 2015 to November 2021 in the online databases European Patent Office and World Intellectual Property Organization. A total of 651 patents were identified for preliminary assessment from the databases and 16 were selected for full reading and discussion. The evaluated patents are focused on the intraarticular route, oral route, and topical route for the treatment of osteoarthritis. Therefore, intra-articular methods show better results and the oral route, which, in turn, is already the most used, is still the fastest and most effective route, especially in relieving pain and discomfort resulting from osteoarthritis. The development of new technologies, such as nanotechnology, allows to envision a promising and positive future in the treatment of osteoarthritis.

Keywords: nanotechnology, osteoarthritis, treatments, patents, symptomatology, pain.

INTRODUCTION

Arthritis is characterized as a disease that affects one or more joints, either acutely or chronically. The signs and symptoms include mainly acute pain, swelling, deformities in the joints, and stiffness [1]. Arthritis has been an increasing prevalence globally and, nowadays, has been the leading cause of disability and earning loss among adults in the United States of America (USA) [2–4]. It has been reported that 37% of USA population have arthritis, including a third of those aged 18 to 64, and an estimated 300 thousand children [4]. Owing to such a high prevalence among population, several research all over the globe are focusing towards identifying the exact etiology of the disease and the cure for the same remains a challenge [2].

Arthritis disease comprises over 100 types, being the most common rheumatoid arthritis (RA), osteoarthritis (OA), psoriatic arthritis, and inflammation arthritis. All the types of arthritis share one common feature which is the impact on the life quality in the affected population [2,5,6]. Also, with combined effects of aging and higher obesity with the increasing numbers of joint injuries, OA is becoming more prevalent, with an estimated 250 million people affected. Therefore, OA is greatly considered as a progressive and degenerative joint disease which is characterized by inflammation, chronic pain, and functional limitation. Besides, this complex chronic disease is also frequently associated with multimorbidity [7].

Despite the physical health injuries, studies have demonstrated that OA may also negatively impact the people's lives in terms of mental health, which includes episodes of suicidal ideation, and loss of perceived memory, since it is mediated by sleep and mood impairments. Moreover, the evidence that OA is a risk factor for cardiovascular disease development has been increasing [8–12]. Due to the impacts of this disease, OA may consume a higher amount of healthcare resources and costs as it paves way for the higher risk of hospitalization and emergency department charges [13].

The most common site of OA is the knee, followed by hand and hip. Moreover, the prevalence of OA depends on the age categories, countries of origin, and gender of the population studied [7]. Consequently, the unpleasant suffering of OA is also considered as person specific, wherein the different biopsychosocial factors modulate inflammatory processes as well as behavioral responses to trigger pain and interact to the disability in various levels in patients. For this reason, the non-surgical treatments are considered the leading management of OA [14]. For instance, the reduction of modifiable risk factors, intraarticular therapy, and physical modalities are gaining attention. However, the OA treatment is focused on the reduction of pain and stiffness, alternative therapies, and the maintenance of physical functioning [15].

Meanwhile, pharmacological therapy also is used in the treatment of OA. According to *American College of Rheumatology* guidelines, paracetamol is the first-choice drug, followed by topical or oral non-steroidal anti-inflammatory drugs (NSAIDs), tramadol or intra-articular corticosteroids injections for additional relief [16]. NSAIDs are found effective for overall pain from OA [15,17]. Furthermore, in the OA treatment, cell and tissue penetration must be balanced with lymphatic clearance, as smaller materials can be removed from the joint more quickly. Thus, the nanomaterial size may offer better control over drug biodistribution, and efficacy compared to macro-scale delivery systems. Also, diverse forms of nanotechnologies are found to deliver different classes of drugs, improving their activity [18].

Nanotechnology has been presenting unique advantages for drug delivery of therapeutics for OA, such as improving drug targeting, enhancing drug solubility and stability, preventing drug dispersion and degradation in body fluids, and extending drug circulation and retention time in the body. Because of these, the increasing development of nanotechnology in drug delivery systems has provided new ideas and methods for OA therapy [19,20]. As such, with the advent of new technologies and promising factors in solving the problems arises a need towards preventing the exploitation of new inventions and innovations.

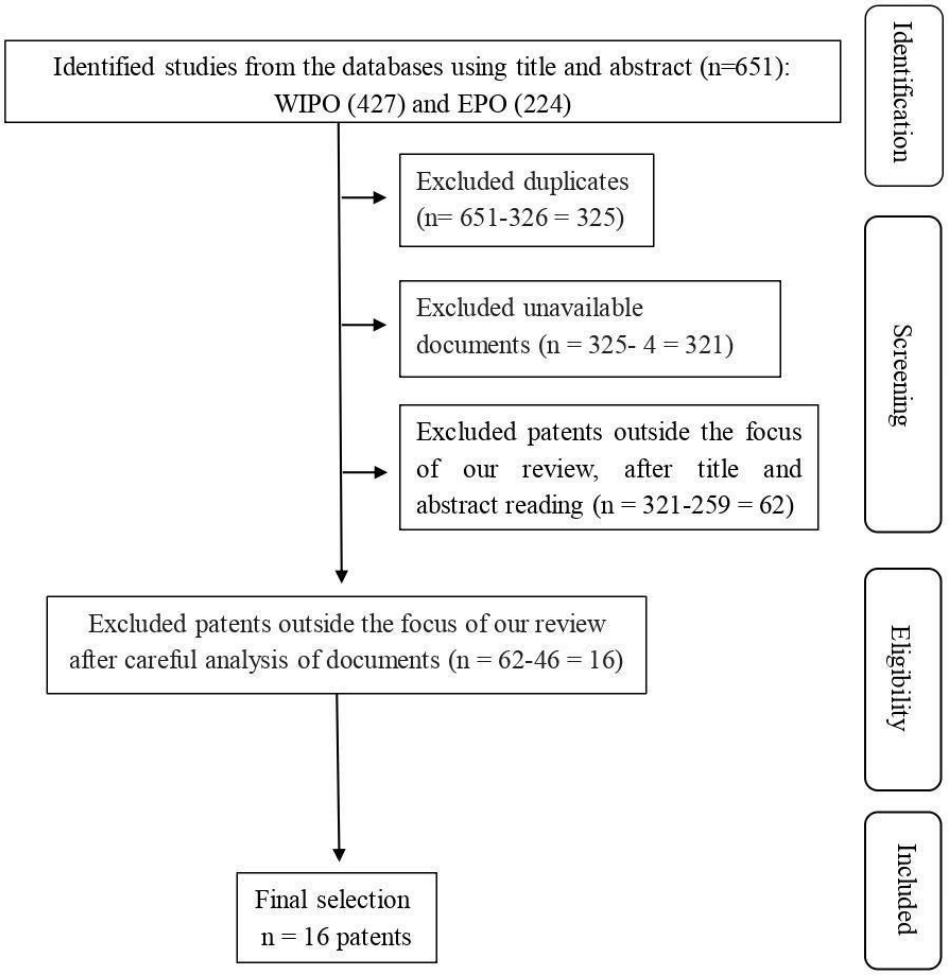
Therefore, substantial attention has been given to the patents nowadays since they are the considerable sources of innovation in the new drug development and therapeutic strategies [21,22]. Thus, this review aims to evaluate patents that have developed innovations, therapeutic strategies, and alternatives using nanotechnology in the OA treatment.

METHODS

The present review shows patents deposited from 2015 to November 2021 in any language. The research was carried out in the free and online database Espacenet, from the European Patent Office (EPO), and World Intellectual Property Organization (WIPO) using the descriptor "nano*" and the code A61P19/02 of the International Patent Classification (IPC). This code refers to drugs for joint disorders, e.g., arthritis, arthrosis. A total of 651 patents were identified for preliminary assessment from the databases, of which 326 were excluded due to duplicity. After reading the title and abstract, 259 patents were excluded because their content fell outside of the focus of this review. Furthermore, we excluded patents about drugs used for other purposes and rheumatoid arthritis, due to the difference in the treatment and mechanism of action of the disease. Following a full reading of the patent, a further 46 were also excluded from being outside the study's scope and four were also excluded because the complete text was not available. Then, 16 patents were selected for full reading and discussion. **Figure 1** illustrates

the patent search guidelines and screening guidelines in this review, based on PRISMA methodology.

Figure 1: Flowchart of patent search and screening.



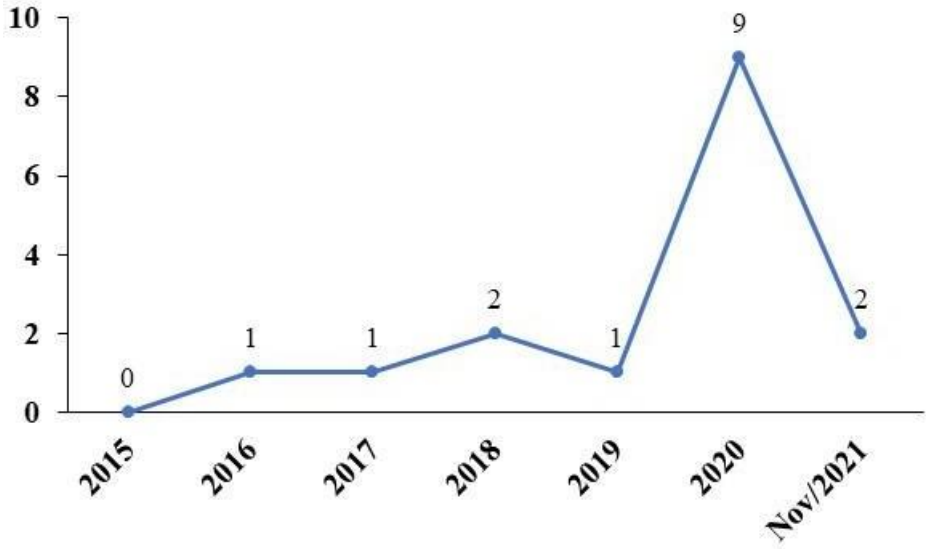
RESULTS AND DISCUSSION

Patents Searching and Screening

Besides the OA was considered as a disease of purely mechanical cartilage degradation, nowadays it is also known as a complex condition affecting the whole joint. Therefore, an improved understanding of the pathogenesis disease associated with the advances in the investigation of biomarkers have increased the ability to identify patients with higher risk of disease, diagnose early OA, and measure treatment efficacy within a short time [22]. In addition, OA remains a public health problem with global impact as it still lacks effective treatment strategies under chronic condition [23].

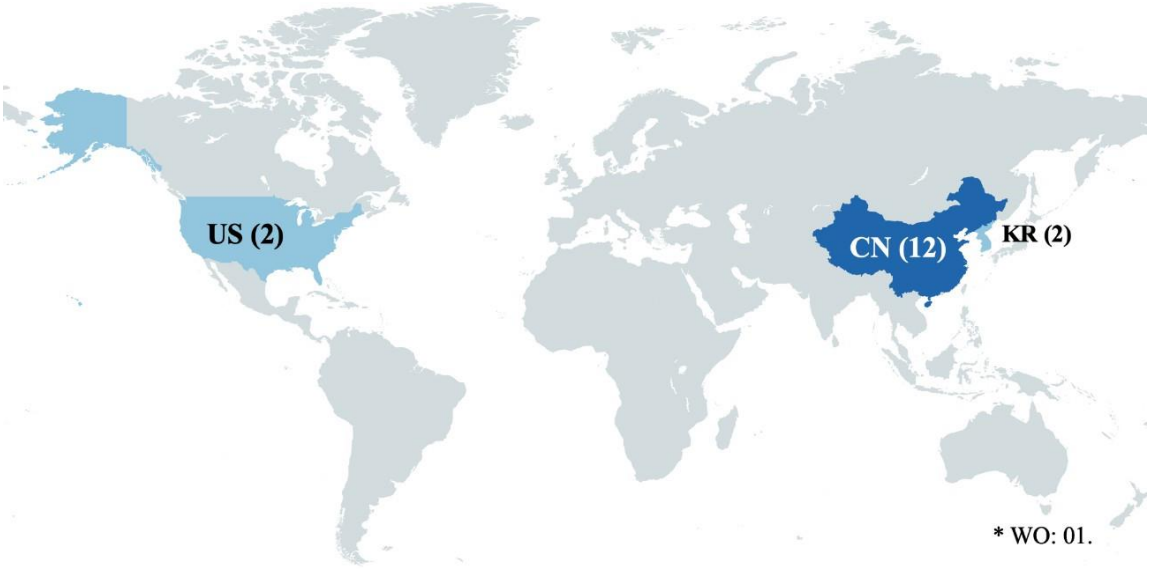
Therefore, the patents of this review covered the period from January 2015 to November 2021, contemplating five years of research and new technologies. According to Figure 2, no patent was selected in the year 2015; however, from 2016 there has been a growth in the number of selected patents. This was probably due to Osteoarthritis Research Society International's (OARSI) call to attention to the cause in 2015, bringing a greater focus to the disease and the development of new technologies. For this reason, since 2018 the number of publications has been increasing, with two documents in this year. In 2020 the highest number of published patents was obtained, with nine documents. However, the number of patents in the year 2021 was not much increased probably because of the delay in the publication process due to the eighteen-month secrecy period that patent applications suffer, becoming unavailable in the databases. Consequently, it was not disposable for analysis.

Figure 2: Number of patents per year of application.



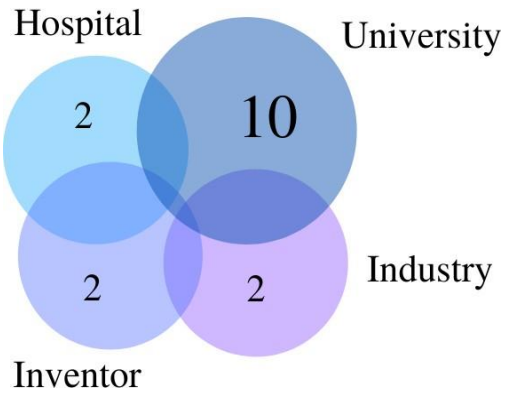
Additionally, according to Figure 3, most of the patents analyzed were filed by the countries China (CN) and the United States of America (USA), with twelve and two patents, respectively. The reason why CN and the USA were generally more present in the publication of patents could be associated to their good economy and high investment in technology and innovation and ensuring the intellectual property in technology research in treating the diseases [24,25].

Figure 3: Final selection of patents: countries. WO: World Intellectual Property Organization.



Moreover, the type of applicants is also a category to divided and classified the patents since various scientific institutions protect an invention using a patent application. Therefore, the university was the biggest applicant with ten patents. Independent inventors, industry, and hospital also appeared as applicants with two patents each one **(Figure 4)**.

Figure 4: Final selection of patents: type of applicants.



Nanotechnology and Administration Routes in the Treatment of OA

OA has been the leading cause of disability in older adults, also being influenced by increasing obesity and aging population. However, while OA is becoming more frequent, the development of new treatment alternatives does not keep pace with this progression. Despite its considerable importance, due to the social determinants, OA is still neglected [26]. Moreover, an incomplete understanding of the OA pathophysiology still prevails, since it differs between the patients, joints localization and disease stage, which increases the difficulty of obtaining an effective treatment target [27].

Nanotechnology is a branch of science which involves the manipulation and control of matter at the nanometer scale to produce new structures, materials, and devices. Also, the nanotechnology is shown to bridge the barrier of biological and physical sciences by applying nanostructures and nanophases at various fields of science both in diagnosis and treatment, especially in nanomedicine and nano-based drug delivery systems. Nano drug delivery systems provide a new drug delivery method for the treatment of various diseases and demonstrate numerous advantages over traditional drug delivery systems [28,29].

Nano drug delivery systems provide advantages in terms of transporting the drug to the target tissue whilst maintaining a concentrated form so that the efficacy of the drug may be maximized following endocytosis. Moreover, the nano delivery systems prevent the dispersion or degradation of the drug by the body fluids leading to enhanced drug circulation or retention time within the body as well as increase the capacity to transport a large volume of drug, increasing the solubility of hydrophobic drugs and the capability of attaching targeting molecules via surface modification to achieve specific delivery [20,30].

Thus, the nanomedicine usually possesses desirable properties, such as biodegradability, non-toxicity, biocompatibility, and high drug encapsulation with the ability of precise site-specific delivery, which have the potential to improve conventional treatments. The nanomedicine can be fabricated from a variety of materials, including synthetic or naturals polymers and biopolymers. Moreover, there have been many types of nanotechnology in the market, such as nanoparticles, dendrimers, liposomes, micelles, and exosomes are examples of nanocarriers that have been. The site of administration has a direct impact on the mechanism of action and outcome, being a critical aspect to consider when addressing the route of administration of nanotechnology drug delivery systems [31,32].

Therefore, **Table 1** has detailed information on the sixteen patent publications selected and evaluated in this review. In short, nine of the evaluated patent publications are focused on the intraarticular route, oral route (five), and topical route (two) for the treatment of OA. Thus, the following section discusses the patent content according to pharmacochemical properties.

Intraarticular route

From the pharmaceutical point of view, the intraarticular route opens a range of possibilities formulation-wise since it presents a rapid clearance of drugs after the administration. For this reason, a variety of sustained release formulations can be developed to deliver drugs and other biologics through this route [33]. Beyond that, when the treatment is injected into the joint, only a small amount of the drug would be required to exert the desired pharmacological activity and decrease the drug exposure to inappropriate sites [34]. The

intraarticular route includes the possibility to achieve high drug concentrations at the site of action with limited systemic toxicity as well as it can be especially important for patients who are unresponsive to oral medications. However, in the past, the intraarticular route has been underestimated in the treatment of joint related disorders, and reliance on the systemic routes of administration prevailed instead [35].

Therefore, Han and Guo (2017) described a medical nanometer material comprised of a nanometer selenium sulfate selenide micelle. In this invention, the chondroitin sulfate A is used as a carrier while the nano-selenium combined with chondroitin sulfate A form the nano-micelles particles by physical adsorption. The nano-micelles of the formulation have an average particle diameter of 85 nm, low toxicity, and high biological activity. Moreover, the chondroitin sulfate nano-selenium provided by the invention is a biodegradable polymer nano-micelle, which has good solubility in water and a better bioavailability. Also, it has been verified that the micelle particles can show the Tyndall effect, indicating that a better colloid is formed [36].

Beyond that, the inventors developed a new type of nano-glue to prevent and cure OA through antagonizing T-2 toxin-induced chondrocyte apoptosis, improving the sub-microstructure (mitochondria, lysosomes) of kappa cell chondrocytes, and promoting cell growth [36]. T-2 toxin is a highly toxic trichothecene mycotoxin and a mold byproduct of *Fusarium* species. T-2 toxin induced apoptosis is a consequence of its toxic effects, which could contribute to the mitochondrial alteration of chondrocytes and cartilage degradation [37].

Peng et al. (2019) also prepared selenium-containing compounds or selenium nanoparticles into local injection preparations, which provides a more rapid, direct, and safe treatment for various joint pains, when compared with oral or long-term external application. The drug efficacy experiment proves that the present invention can significantly reduce the level of inflammatory cytokines in the joint lavage fluid of the arthritis model, and its therapeutic effect can even reach the curative effect better than that of the positive drug. Given this, the present invention has good clinical application prospects [38]. Clinical and epidemiological studies suggest that selenium is an important nutrient for muscle health since its deficiency has been associated with muscle pain, weakness, deleterious effects on muscle mass, and strength, which are reversed with selenium administration [39].

In 2018, Ding et al. developed a nanovesicle coated with vitamin D and vitamin K, vitamin D3 (cholecalciferol) and menaquinone- 7, respectively. The direct delivery of both vitamins to the blood can increase the efficacy at least several tens of times compared to conventional oral preparations. Besides that, the invention also is composed of vesicle adjuvant lecithin-based liposomes, which are extracted from plants or animals. For this reason, the

clinical efficacy of OA is greatly enhanced, and the preparation has almost no toxic and side effects [40].

The use of vitamins in the treatment of OA is a parallel alternative in containing the damage of this disease since the vitamin D supplementation increases muscle strength, improves physical function, and decreases the risk of falls among older people with low level of serum vitamin D [41]. Moreover, vitamin K, as a dietary component, can influence cartilage calcification through carboxylation of Matrix gamma-carboxyglutamic acid protein (MGP), which is expressed in chondrocytes and develops spontaneous calcification of the blood vessels [42].

Long et al. (2019) aimed to provide an application of nano-synthesis enzymes to promote polymer hyaluronic acid (HA) synthesis in cells. The nanoparticles have a particle diameter of 100 to 200 nm and a pore diameter of 10 to 60 nm, and the mesoporous is composed of silicon inorganic nanoparticles. Besides that, the invention firstly modifies the nanoparticles, greatly improves the drug-loading ability of the nanoparticles to the macromolecular hyaluronan synthase and transfers the nanoparticle-hyaluronic acid synthase loading system into synovial cells and articular disc cells. Moreover, the nanoparticle-hyaluronic acid synthase loading system can promote the migration of the target protein to the plasma membrane, so that the content of HA in synovial cells increases. Therefore, with good development and application prospects, the number of clinical injections of exogenous hyaluronic acid can be greatly reduced, as such the anxiety of patients is greatly reduced, and the number of diagnosis and treatment is saved [43].

Thus, intraarticular HA is a local treatment without systemic adverse events, being an alternative to analgesics and NSAIDs in patients with comorbidities as well as a secondary option in case of inadequate response to first-line pharmacologic OA treatments. Beyond that, intraarticular HA is currently used for symptomatic treatment of OA [44].

Xue et al. (2020) developed a dual-drug-loaded nano-microsphere with photothermal response characteristics of targeted cartilage. The nano-microsphere has a diameter of about 50 nm and can effectively penetrate the dense type II collagen network and improve the nano-microsphere cartilage retention time. The invention combines the responsive effect of near-infrared laser stimulation, which can absorb 808 nm near-infrared, and has an efficient photothermal conversion effect. Therefore, the surface is modified by the type II collagen targeting polypeptide, which can realize the active penetration of nanomaterials into cartilage tissue and facilitate the absorption of cartilage cells. The nanomaterial not only provides the possibility of targeted therapy for early and mid-term OA, but also enables real-time monitoring

of the targeted therapy effect of nanomaterials. For this reason, the invention adopts a preparation method with simple synthesis technology, fast preparation cycle, simple test equipment, and easy mass production to prepare cartilage-targeted dual-drug-loaded nanospheres [45].

Beyond that, the dual-drug-loaded nano-microspheres have optical properties. Thermal response characteristics, nuclear magnetic imaging, photothermal imaging and other characteristics can achieve effective monitoring of *in vivo* therapeutic effects and controlled release of drugs, and the ability to target chondrocytes in cartilage tissue is strong and stable. The invention has the advantages of good biocompatibility and can significantly delay cartilage degeneration in animal models. Moreover, the multifunctional composite nano-microspheres prepared by the present invention have the characteristics of small particle size, good biocompatibility, strong cartilage targeting, and photothermal stimulus responsiveness to control drug delivery [45].

Khang et al. (2020) provided an exosome nanocarrier composition characterized by containing an exosome as a main component and a differentiation factor, as an auxiliary component. Differentiation factors of the present invention may be cartilage differentiation factors including microRNAs (miRNAs), dexamethasone, transforming growth factor-β1 (TGF-β), and the miRNAs are miRNA-27a, miRNA-27B, miRNA-140, and miRNA-146. The invention has advantages as a good cell therapeutic agent, such as cell proliferation and differentiation and a carrier as a protective agent for protecting the intrinsic properties of substances from immune responses. Moreover, the invention has excellent biocompatibility than other existing carrier materials, protects the intrinsic properties of the material, and expresses a regenerative effect on cartilage damage at the site, as well as OA [46].

Exosomes are released by different types of cells and contain a variety of functional units mainly proteins, nucleic acids and lipids. Based on their endogenous properties and multifunctional abilities, these lipid bilayer membrane vesicles have generated much recent interest in the search for medicines and pharmaceutical interventions. Exosomes play central roles in cell-cell communication that result in the modulation of several pathophysiological pathways. Exosomes consist of varying composition of macromolecules mainly protein, miRNAs, messenger RNAs (mRNAs) and lipids. Exosomal miRNA takes part in modulating gene expression in relation to stem cell differentiation [47].

Sharma et al. (2020) created bioactive nanoparticles composed of stabilized manganese dioxide (MnO_2) with a weighted size of 60 nm, which can scavenge reactive oxygen species to decrease oxidative stress. The nanoparticles disclosed in the invention are non-toxic to

chondrocytes and scavenge reactive oxidative species (hydrogen peroxide) to reduce oxidative stress on tissues such as cartilage, in order to modulate joint pain and inflammation. The MnO_2 nanoparticles protect cartilage from interleukin-1β-induced glycosaminoglycan loss and the production of nitric oxide. MnO_2 nanoparticles will protect cartilage from inflammation-induced oxidative stress in both an in vitro cytokine-challenged cartilage system and an *in vivo* animal model of post-traumatic OA (PTOA). Moreover, the use of engineered small (less than 15 nm), cationic MnO_2 nanoparticles facilitated uptake and penetration through cartilage and increased their chondroprotective capacity. Since the nanoparticles show intracellular localization in chondrocytes, they also can deliver other chondroprotective agents including nucleic acids to target multiple pathways in the OA pathology [48].

Sharma and Brown in 2021 also proposed a drug delivery system composed of a chondrogenic or chondroprotective agent encapsulated in nanoparticles and an effective amount of a bioadhesive agent to adhere the delivery vehicle to a cartilage surface in the joint of a subject. The bioadhesive can be any natural or synthetic molecule capable of binding to cartilage in a joint. The nanoparticle in this invention is biodegradable and demonstrates high retention and cytocompatibility since the size range can be between 50 to 90 nm or 150 to 250 nm [49].

In this same year, Mu et al. related a pH-sensitive microsphere carrying sodium hyaluronate gold nanoclusters. The invention used a pH-sensitive biodegradable polymer material as a skeleton, and the inside of the microspheres wraps the gold nanoclusters loaded with sodium hyaluronate. Sodium hyaluronate is a natural polysaccharide that can specifically bind to CD44 receptors, and CD44 is widely distributed in epithelial cells and activated. When the adhesion receptors on lymphocytes are exposed to various inflammatory stimuli, the expression of CD44 on leukocytes and activated macrophages increases rapidly. Therefore, sodium hyaluronate targets macrophages to improve efficacy. This preparation can not only achieve the purpose of slow release of drugs, but also has the performance of precise targeted treatment of inflammation. It can effectively solve the problems of frequent injections and low bioavailability in the treatment of osteoarthritis and has strong research significance [50].

Oral route

Oral route is the most common form of drug administration due to its advantages. For example, the convenience of drug administration via oral route is often patient preference, which is generally higher than other routes, and cost-effectiveness, because of the ease of large-scale manufacturing of oral dosage formulations. However, this route can be particularly challenging when considering the variations that occur in the absorption of a molecule due to

interaction with gastric contents and secretions, membrane permeability, and intestinal transit. Also, the development of oral formulations presents several challenges, that are mainly attributed to the physicochemical properties of drugs, including poor water solubility and membrane permeability. For these reasons, more attention has been given to the nanotechnology since it can solve those issues presented in the formulations [51,52].

Ding et al. (2018) related a preparation composed of Celecoxib (CXB) encapsulated in nanocrystal. CXB is a selective NSAID indicated for the treatment of signs and symptoms associated with OA since it has a high efficacy in relieving pain and inflammation [52]. The raw material drug used in the invention has an initial particle diameter of 50 to 100μm. Moreover, the nanocrystals are nanosized crystals of drug particles stabilized by surface stabilizers, presenting a reduced size and increased surface area. Because of these characteristics, the nanocrystals improve the water insolubility of CXB, consequently enhancing its oral bioavailability and dissolution. Beyond that, the use of nanocrystal provides the fastest breakthrough from design development to commercial production [53,54].

Two years later, Wang et al. (2020) used the same train of thought, but in this case, they encapsulated Piroxicam (PRX) in nanocrystals. Therefore, PRX is an NSAID used for the relief of OA, and its recommended dose in adults is 20mg daily, due to the higher risk of adverse events. Besides that, the therapeutic effects are seen early, taking up only 12 days to reach the steady state levels [55]. For the same reason as Zhuang et al. (2018), they sought to increase the dissolution rate, bioavailability and enhance the stability of the invention. Because of this, PRX nanocrystals could be released more than 80% of the drug in five minutes [56]. Moreover, Lai et al. (2014) also obtained a new formulation with PRX nanocrystals with a drug dissolution profile faster than those NSAID currently available on the market [57].

Xiang and Zhao (2020) related an invention composed of a *poly lactic-co-glycolic acid* (PLGA) nanosphere loaded with a pyridine oxide derivative. The invention demonstrated considerable results since the animal test had a satisfactory effect on arthritis. The improvement effect of mouse model rat paw arthritis severity is also significantly better than that of free pyridine oxide derivatives. PLGA has good biocompatibility and is currently the most used biodegradable polymer material for preparing nano and microspheres [58]. This happens because of its long clinical experience, favorable degradation characteristics, possibilities for sustained drug delivery, well-known biocompatibility, which can improve the nanospheres physicochemical characteristics [59,60].

Cai et al. (2020) presented nanoparticles composed of Prussian blue, which presented the cavity diameter between 1 to 90 nm. The invention can reduce interleukin—β (IL-1β)-

induced inflammatory response in human chondrocytes, inhibit ECM degradation and apoptosis of human chondrocytes, and inhibit IL-1-induced nuclear factor kappa B (NF-κB) signal activation by down-regulating of the protein Rac1. Consequently, it also delays the progress of OA in the body. The Prussian blue nanoparticles have stable physical and chemical properties, simple preparation, easy preparation, and the like, and have broad clinical application prospects in the treatment of arthritis [61].

Beyond that, Prussian blue nanoparticles are a nanomaterial with unique properties and an excellent biocompatibility due to this they can be synthesized in mild conditions. These nanoparticles also can be derivatized with polymers and biomolecules. Prussian blue nanoparticles have been used in biomedicine as therapy and diagnostic agents since they can act as drug carriers, antidotes, adsorbents, contrast agents, photothermal agents, and nanoenzymes [62].

Im and Kang (2016) proposed an invention composed of Kartogenin (KNG) or an anti-inflammatory analgesic, such as diclofenac, nanocomposites covalently linked in sequence, and double thermosensitive drug carrier containing the drug encapsulated in the complex. This invention could promote the regeneration of cartilage, through the KNG's mechanism of action since it is a small molecule capable of enhancing the chondrogenic differentiation of human mesenchymal stem cells (hMSCs). This happens because KNG interacts with actin-binding protein filamin A (FLANA), core-binding factor β (CBFβ), and transcription factor RUNX1. Consequently, these interactions enhance the synthesis of cartilage matrices, such as collagen type II (COLII) and aggrecan [63]. Moreover, it has a temperature sensitive ability, which controls the drug release behavior. Therefore, this action is essential due to the high use of cold compress therapy by OA patients [64].

Topical route

Oral therapies were traditionally recommended for patients with knee OA pain, which includes paracetamol and NSAIDs. However, these treatments bring some issues to the patient, such as hepatotoxicity, age dependent risks of gastrointestinal, cardiovascular, and renal adverse events. Due to this, the interest in alternative therapies for OA management is increasing, including the topical therapies [65]. Topical therapies have been defined as those designed to act locally. Topical administration generally has less gastrointestinal toxicity than oral and it is considered relatively safe. However, the skin adverse effects cannot be ignored when happened [66–68].

Zhang and Xie (2020) invented a nano-speed paste cold compress gel, which is composed of a mixture of extracts, such as mint extract, wintergreen extract, and white fungus

extract. All the extracts are in the form of powder, having a particle size between 2 nm to 15 nm. The innovation could penetrate the skin and the periosteum to reach the lesion in 10 or 30 minutes. Moreover, the gel is layered and suspended in human tissues, and it quickly takes effect after reaching the lesion, continues to be absorbed, has deep analgesic, long-lasting anti-inflammatory effects, and has good treatment for bone and knee osteoarthritis, in which the joint pain rate is 91%, and the improvement rate is 9%. Beyond that, the nano-speed paste cold compress gel does not present liver and kidney metabolism, toxic and side effects [69].

Due to uncertainty regarding the treatment and the high heterogeneity of the disease pathology, there is a continuous interest in identifying natural products that safely promote joint health. Among natural products, the polyphenol class is well-known to posses' anti-inflammatory activities, being important to OA treatment [70]. Despite the advantages and innovation, when referring to the use of natural products, these generally have low water solubility, reduced stability and lack of direction, less bioavailability and increased systemic clearance. Therefore, repeated administrations or higher doses are necessary, which makes the drug a poor candidate for therapeutic use. Thus, several drug delivery systems, such as liposomes and nanoparticles, are used to circumvent the physicochemical limitations of these compounds [71,72].

In the same year, Cai et al. provided a nanogel drug carrier that targets the delivery and consumption of a large amount of Hydrogen peroxide (H_2O_2) and simultaneously releases carbon monoxide (CO). Based on the existence of many activated macrophages around OA, the activated macrophages secrete a large amount of H_2O_2 inducing the transformation of normal macrophages to activated macrophages. Therefore, the invention selects the CO released in the presence of a large amount of H_2O_2, as an anti-inflammatory drug to combat the resistance of OA Inflammation treatment, since it is more easily phagocytosed by activated macrophages. CO is an endogenous anti-inflammatory function small molecule, easier to penetrate the cell membrane, improve the activation of cell anti-inflammatory signaling pathways and the secretion of anti-inflammatory factors. For the anti-inflammatory drug to be delivered to the site of inflammation, the invention used folic acid-modified hyaluronic acid as a targeting material to wrap around the nanogel. The nanogel presented a size between 240 to 280 nm [73].

CONCLUSION

With the increasing prevalence of arthritis worldwide OA is considered more specific being a progressive and degenerative joint disease characterized by inflammation, chronic pain and functional limitation. The search for a cure and/or treatments that involve not only

impacting the signs and symptoms of the disease become increasingly necessary. Therefore, the option for medium and long-term therapies capable of alleviating the degenerative process of OA has strong significance, as they point to a possible cure or considerable improvement in the quality of life of arthritic patients. Therefore, intra-articular methods show better results, if we consider that these inventions are willing to directly impact the pathophysiology of the disease. However, the oral route, which, in turn, is already the most used, is still the fastest and most effective route, especially in relieving pain and discomfort resulting from OA. Despite that, the development of new technologies, such as nanotechnology, allows to envision a promising and positive future in the treatment of OA.

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Disclosure statement

The authors report there are no competing interests to declare.

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Table 1. Nanotechnology for OA treatment, technical patent information.

Patent number	Inventor/ Year/Country	Nanoparticle type	Polymer	Particle Size (nm)	Drug/ Substance	Route of administration	Purpose of system	Outcomes	Reference
CN107260668A	Han Jing and Guo Xiong, 2017/CN	Nanomicelles	Biodegradable polymer	85	Chondroitin sulfate A, Selenium, L-ascorbic acid.	Injectable	Decrease toxicity and increase biological activity	Double pharmacological activity, reducing the toxicity of inorganic selenium, improve its bioavailability combined with the biological activity of chondroitin sulfate A	[36]
CN111686081A	Xiang Fei and Zhao Zhixin, 2020/CN	Nanosphere	PLGA	10 to 1000	Pyridine oxide derivative	Oral solid preparations, oral liquids and injection dosage forms.	Improve pyridine oxide activity	Significantly stronger inhibitory effect on various subtypes of JAK and improvement significantly of effect of rat paw arthritis severity than that of free pyridine oxide derivatives	[58]
CN111110436A	Zhang Dezhu and Xie Xiaolin, 2020/CN	Nano-gel	NS	2 to 15 (particle sizes of the powders)	Mint extract, wintergreen extract,	Topical	Provide a nano-speed paste cold compress gel with quickly effect after reaching	The invention was good curative effect on different types of	[69]

					Tremella extract, castor oil.		the lesion and deep, long-lasting effects	muscles and bones and arthritis, in which the joint pain rate was 91%, and the improvement rate was 9%	
WO2016064202 A1	Im Gun Il and Kang Mi Lan, 2016/WO	Nanoparticles	Pluronics	NS	Kartogenin or Diclofenac	Oral or parenteral	Double drug delivery system comprising a drug encapsulated in the complex	Promoted cartilage regeneration effect through sustained release	[64]
CN108542886A	Ding Zhuang et al., 2018/CN	Nanocrystal	PVP, PVP VA, Soluplus®	10 to 1000	Celecoxib	Oral	Improving water insolubility of celecoxib and improving its bioavailability	Celecoxib nanocrystal preparation of can achieve 80% dissolution within 50 min; significantly improved the dissolution and oral bioavailability of celecoxib	[55]
CN111840231A	Wang Wenxi et al., 2020/CN	Nanocrystals	Polyacrylic	200 to 500	Piroxicam	Oral	Provide an economical, efficient, green and environmentally friendly method for	The piroxicam nanocrystals prepared by the method have extremely high dissolution rates, good	[57]

							preparing piroxicam nanocrystals	stability, and can be released within 5 minutes more than 80% of the drug, thereby improving the bioavailability	
CN109276712A	Long Xing et al., 2019/CN	Nanoparticle	Polyethyleneimine	100 to 200	Hyaluronic acid (HA)	Intra-articular injection	Provide an application of nano-synthesis enzyme to promote polymer hyaluronic acid synthesis in cells	The results showed that HA synthase can carry into the synovial cells in the joint cavity through porous nanomaterials, which can promote the synthesis and secretion of HA. Thus, synthetic enzyme loading system provides a new means for the efficient treatment of OA.	[43]
CN109044974A	Ding Changhai et al., 2018/CN	Nano vesicle/ liposomes	NS	NS	Vitamin D and vitamin K	Parenteral	Provide a nano vesicle preparation coated with vitamin D and vitamin K and your application for treating OA	The direct delivery of vitamin D and vitamin K to the blood can increase the efficacy of at least several tens	[40]

								of times compared to conventional oral preparations.	
US10993919B2	Sharma Blanka and Brown Shannon B et al., 2021/US	Nanoparticles	PVA, PLGA	5 to 750	Kartogenin or PDGF-BB	Intra-articular injection	Drug delivery system that comprises a chondrogenic or chondroprotective agent contained within a delivery vehicle and an effective amount of a bioadhesive to adhere the delivery vehicle to a cartilage surface in the joint of a subject	Healthy cartilage had significantly more NP retention than OA tissue. Cationic PLGA NPs had significantly more retention than anionic PLGA NPs for both healthy and OA tissue.	[49]
US2020390806A1	Sharma Blanka et al., 2020/US	Nanoparticles	PEG	1 to 250	MnO_2	Injection	Bioactive nanoparticles (NPs) that can scavenge reactive oxygen species (ROS) to decrease oxidative stress	MnO_2-NP can reduce oxidative stress in osteoarthritic cartilage. Given their joint retention time and ROS scavenging capacity, these NPs can target oxidative stress to treat or prevent OA. They also	[48]

								can deliver other chondroprotective agents to target multiple pathways in the OA pathology	
CN110742856A	Cai Xiaojun et al., 2020/CN	Nanogel	EDA	240 to 280	Dendritic Polypeptide, COR M401, and Hyaluronic Acid	N. S	Nanogel drug carrier that targets the delivery and consumption of a large amount of H_2O_2 and simultaneously releases CO	Controlled loading of CORM401 was achieved by regulating the amount of CORM401 input. The surface of the nanogel was successfully coated with folic acid-modified hyaluronic acid to form a targeted delivery and consume a large amount of H_2O_2 while releasing CO	[73]
CN110917209A	Peng Yongbo et al., 2020/CN	Nanoparticles	Carbomer 940 and Polysorbate 80	20 to 60	Selenium	injection	Provide a use of selenium-containing compounds or selenium nanoparticles in the preparation of injections or microneedles for treating arthritis.	Selenium-containing compounds and selenium nanoparticles have significant anti-gout arthritis effects, and the effect of protein binding nano-selenium is the most obvious.	[38]

CN112023060A	Xue Song et al., 2020/CN	Nano-microsphere	TMB	50	MPDA	injection	Provide a dual-drug-loaded nanosphere with photothermal response characteristics for targeting cartilage	The multifunctional composite nanospheres have small particle size, good biocompatibility, strong cartilage targeting, and photothermal stimulus responsiveness to control drug delivery	[45]
CN111632067A	Cai Xiaojun et al., 2020/CN	Nanoparticles	PVP	30 to 200	Prussian blue	oral	Prussian blue can reduce IL-1β-induced, inhibit ECM degradation and apoptosis of human chondrocytes	The prepared PBzyme has the advantages of stable physical and chemical properties and has broad clinical application prospects in the treatment of arthritis.	[61]
KR102123903B1	Khang Gilson et al., 2020/KR	Exosome nanocarriers	N. S	10 to 200	Exosome and miRNA 140	injection	Exosome-nanocarrier containing a differentiation factor, and using it to cartilize BMSCs, regenerating damaged cartilage	Provide a more suitable microenvironment for the growth of chondrocytes.	[46]
CN113082002A	Mu Hongjie et al., 2021/CN	Nanoclusters and microsphere	PEI	N. S	Folic acid	injection	Provides a new type of sustained-release preparation that can target the treatment of	Nanocluster microspheres prepared by the present invention can	[50]

				OA, solve the sudden release of drugs and the frequency of frequent medications	effectively solve the requirement of frequent injection of ordinary sustained-release preparations to achieve the purpose of slow release.

Abbreviations: JAK: Janus Kinase; NS: Not specified; OA: Osteoarthritis; PDGF-BB: platelet-derived growth factor; PEG: polyethylene glycol; PLGA: poly(lactic-co-glycolic acid); PVA: polyvinyl alcohol; PVP: polyvinylpyrrolidone; PVP VA: vinylpyrrolidone-vinyl acetate copolymer; PEI: Polyethyleneimine; BMSCs: Bone marrow-derived mesenchymal stromal stem cells; TMB: 1,3,5-trimethylbenzene; MPDA: Polydopamine; EDA: Ethylenediamine; IL-1β: Interleukin-1-beta; ECM: Extracellular Matrix; Carbon COR M401: Monoxide; MnO_2 :Manganese dioxide; H_2O_2: hydrogen peroxide; CO: Carbon monoxide.

Countries: CN: China; WO: World Intellectual Property Organization; KR: Korean Republic; US: United States

CAPÍTULO II

Technological prospection of non-pharmacological devices for the treatment of osteoarthritis symptoms through patent review

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Technological prospection of non-pharmacological devices for the treatment of osteoarthritis symptoms through patent review

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ABSTRACT

Osteoarthritis is considered the most common disease of the musculoskeletal system and leads to functional decline and quality loss of life. Providing a better quality of life for patients is the priority, and because of that the osteoarthritis treatment is divided into pharmacological, and surgical. Non-pharmacological treatments have been receiving a lot of attention in recent decades since include associate therapies using physical therapy devices. However, the information is not specific about the content, intensity, frequency, timing, duration and mode of delivery of each non-pharmacological option. For this reason, this review aimed to identify patents that evaluated the effect of physiotherapy devices in the management of osteoarthritis symptoms. The review shows patents deposited from 2010 to April 2022 of the online database Espacenet from the European Patent Office and World Intellectual Property Organization. Therefore, the final selection involved 57 patents that were in line with the study objective. The selected patents were classified in years, country, and type of applicant. In this context, 2015 was the year with the most patent applications, China and industry as the mainly country and type of applicant. The selected patents were also classified in the type of therapy used in the devices, such as therapeutic electrical stimulation, phototherapy, ultrasonic therapy, magnetotherapy, electromagnetic therapy, thermotherapy, associated therapies, and other therapies. Besides that, the needing to develop new technologies for managing OA symptoms is still current.

Keywords: Devices, Pain, Patents, Osteoarthritis, Symptoms, Treatments

INTRODUCTION

Osteoarthritis (OA) is considered the most common disease of the musculoskeletal system and leads to functional decline and quality loss of life [1]. Clinically, OA is characterized by tenderness, joint pain, stiffness, crepitus, limited movement, and local inflammation [2–4]. It's estimated that 250 million people live with OA in the world and that in the United States an annual expenditure of US$ 303 billion is generated, which has 30 million adults with this disease [5–8].

Providing a better quality of life for patients is the priority, and because of that, it created the international recommendations for the management of OA that divide the forms of treatment into three: non-pharmacological, pharmacological, and surgical [9]. The drugs that are commonly used in the pharmacological treatment are non-steroidal anti-inflammatory drugs (NSAIDs), which relieve symptoms. However, their effects in some cases are moderate and safety aspects, which restrict the use of these drugs, especially in older people [10–12].

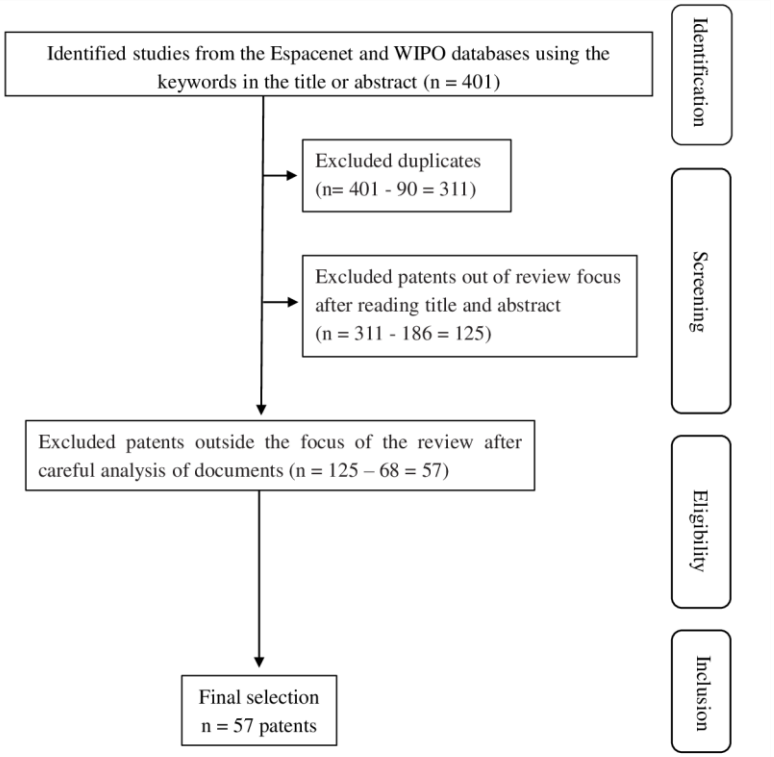
Non-pharmacological treatments have been receiving a lot of attention in recent decades since include orthoses, insoles, exercise, diet and patient education [13]. However, the information is not specific about the content, intensity, frequency, timing, duration and mode of delivery of each non-pharmacological option [14]. The decreasing of the pain and inflammation can be optimized by some devices, such as High Intensity Laser Therapy (HILT), transcutaneous electrical nerve stimulation (TENS), neuromuscular electrical stimulation (NMES), pulsed stimulation (PES), non-invasive interactive neurostimulation (NIN), and other [15–19].

Due to the enchancement in life expectancy, overweight rates and reduced mobility of the world population, the number of OA diagnoses has been increasing worldwide [20]. Therefore, the search for new therapeutic alternatives and consequently devices that help physical therapists has been an emerging demand. As a result, since patents are important sources of invention, they have received a lot of attention recently. Because of this, understanding the trends in the creation of new drugs and therapeutic approaches requires a close examination of their substance [21]. In this context, the present study aimed to identify patents that evaluated the effect of physiotherapy devices in the management of OA symptoms.

METHODS

The present review shows patents deposited from 2010 to April 2022 in any language, of the online database Espacenet from the European Patent Office (EPO) and World Intellectual Property Organization (WIPO), using the descriptors “arthritis or arthrosis or osteoarthritis” and the code A61N of the International Patent Classification (IPC). This code refers to electrotherapy; magnetotherapy; radiation therapy; ultrasound therapy. A total of 401 patents were identified for preliminary assessment, of which 90 were excluded due to duplicity. Furthermore, we excluded patents about devices used to treat other diseases, such as rheumatoid arthritis, fibromyalgia, immunosuppression, and infectious diseases, due to the difference in the treatment and mechanism the disease. The reading of the title and abstract was performed by three evaluators, who excluded 186 patents, in consensus, because their content fell outside of the focus of this review. Following a full reading of the patent, a further 68 were also excluded from being outside the study's scope. The final selection involved 57 patents that were in line with the study objective. **Figure 1** illustrates the patent search guidelines and screening guidelines in this review, based on the PRISMA methodology.

Figure 1: Flowchart of patent search and screening.

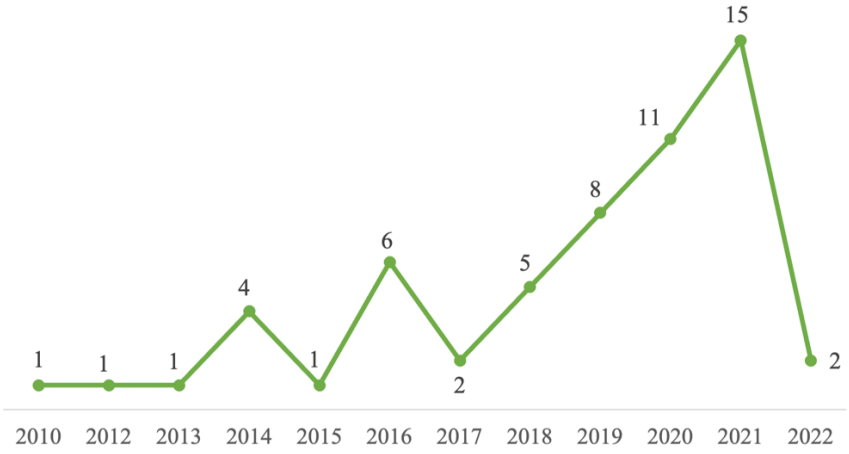


RESULTS AND DISCUSSION

Patent searching and screening

Initially, we classified the patents according to the year of publication, they covered a period from 2010 to February 2022. In the first five years interest in deposits was low, except for 2014. From 2015 onwards there was an increasing increase until 2022, excluding the years 2017 and 2022 **(Figure 2)**. This can be justified by the fact that OA is considered the most common joint disease worldwide, with increasing incidence and prevalence related to increasing age. This endemic disease affects about 30 million adults in the United States and 300 million around the world [22,23]. In this way, since 2018, the number of patents deposited related to this health problem has increased until 2021 with 15 documents. However, in 2022 only two patent applications were found focusing on the research topic. This fact can be attributed to the 18-month period of secrecy that patent applications suffer when they are submitted for protection.

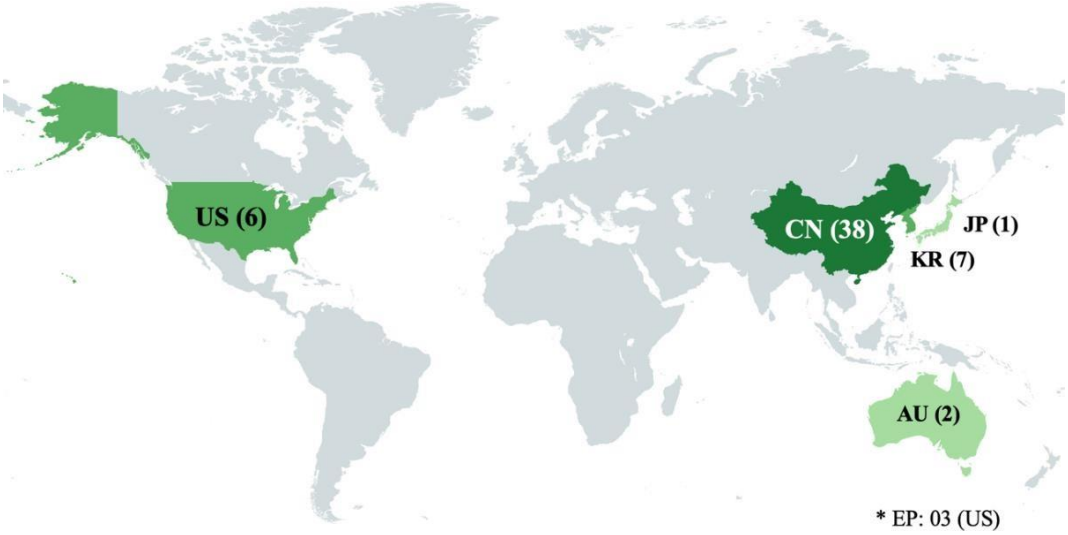
Figure 2. Distribution of patents by publication year.



Another evaluated aspect of the selected patents corresponded to the countries of origin of the filed patents. Among these are China (CN) leading the ranking with 38 documents, followed by the Republic of Korea (KR) with seven, the United States of America (US) with six, the European Patent Office (EP) with three, Australia with two, and Japan only one patent **(Figure 3)**. The oldest deposit made in 2010 is of Chinese origin, and the two most recent in 2022 belong to the United States and China. As expected, China often tops the list of countries with the highest activity in filing patents, trademarks, and industrial designs. According to the World Intellectual Property Organization (WIPO), this country filed 1,441,086 patent applications in 2020, followed

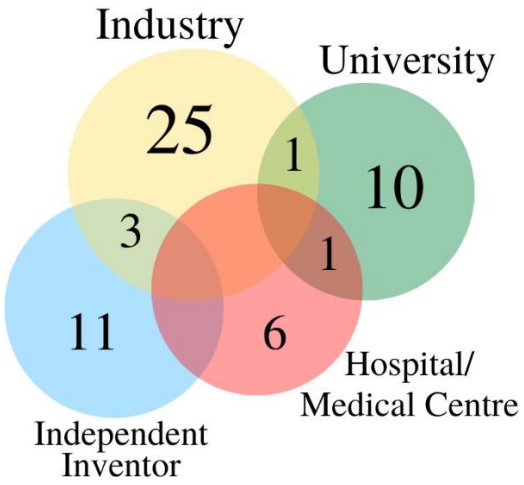
by the United States (496,123), Japan (423,264), the Republic of Korea (260,614), and Germany (168,092) [24,25]. Thus, countries like these make high investments in the Research and Development sector, to improve the technological status and promote innovation to fill the existing gaps in society in the face of demands in the health sector.

Figure 3. Distribution of patents by applicant country. US: United States, CN: China, JP: Japan, AU: Australia, KR: Republic of Korea



In the process of developing an invention, several scientific entities can contribute to the final objective. Unsurprisingly, industries hold the largest number of deposits due to the high capital they have and use them to develop new products to be launched on the market. Our search registered 25 documents deposited by the industrial sector, among these companies are Sichuan Taiyou Technology Co., LTD (CN); Sublimed (US); Valencia Technologies Corporation and Valencia Bioscience, Inc. (US); Biomagnetic Sciences LLC (US); Bionics Co., LTD. (KR). The strong presence of the private sector can be attributed to the size of the global market for therapies for OA **(Figure 4)**. This market was valued at around US$ 6.7 million in 2020, with a forecast of US$ 15.7 million by 2030. Factors such as high prevalence of the disease, increased funding in the private and government sectors and advances in R&D activities in the development of treatments are the main reasons for the growth of the OA therapeutics market [26].

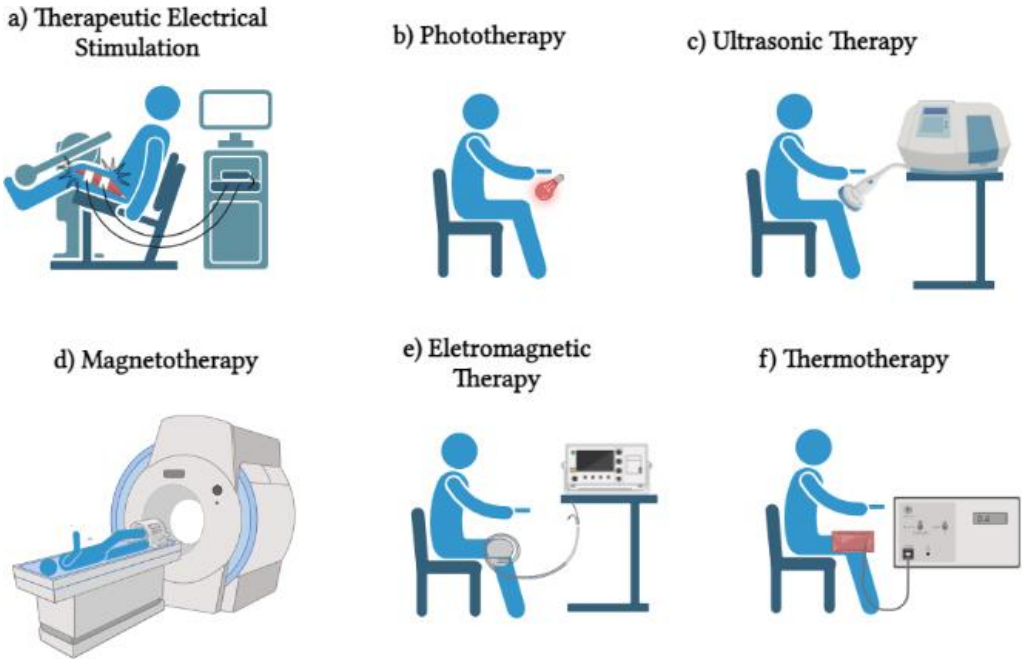
Figure 4. Distribution of patents by applicants type.



In addition to the private sector of industries, universities can deposit their inventions developed in their academic environment. In this case, there were ten patent documents carried out by this entity, as an example, we have Sichuan University (CN), Taiyuan University of Science and Technology (CN), Shaanxi University of Chinese Medicine (CN). Another type of scientific entity responsible for several patent applications are independent inventors with 11 applications for protection. As well as hospitals and Medical Centre also applied for invention protection in six documents. Finally, partnerships were established and observed in the selected patents, of which were deposited by the industry partnership with an independent inventor, industry with university, and university with medical centre/hospital, with one document each.

Therefore, the following section is divided in relation to the types of treatments present in the devices and patents will be discussed based on these topics, as shown in **Figure 5.** In this way, the section is subdivided into therapeutic electrical stimulation, phototherapy, ultrasonic therapy, magnetotherapy, electromagnetic therapy, thermotherapy, and associated therapies

Figure 5. Devices associated for the management of OA symptoms.



Therapeutic Electrical Stimulation

Therapeutic electrical stimulation (TES) is a non-invasive treatment modality that involves multiple stimuli delivered superficially, usually using electrodes placed on the skin [27]. TES has been widely used for rehabilitating, treating, and training patients with OA. Its use aims to facilitate changes in muscle action and performance, improve the musculature's strength to be applied by increasing range of motion, reduce edema, decrease muscle atrophy, assist in tissue healing and reduce pain in general [28].

There are different forms of TES, including transcutaneous electrical stimulation (TENS), neuromuscular electrical stimulation (NMES), interferential current (IFC), pulsed electrical stimulation (PES), non-invasive interactive neurostimulation (NIN), functional electrical stimulation (FES), current Russian (RC), among others [29,30]. Widely disseminated in the clinical environment, TENS has several studies that prove its effectiveness, mainly in acute and chronic pain relief, which is provided in two different dosages, high frequency (50 and 100 Hz) and low frequency (2 and 10 Hz). Moreover, the correlation between the clinical picture and the choice of frequencies is fundamental for the effectiveness of the treatment [31,32]. **Table 1** describes the 12 patents that use this therapy as a form of treatment.

Table 1. Main patents that describe Therapeutic Electrical Stimulation devices.

Publication Number	Year	Country	Priority articulation	Rest/Movement Use	Device	Electric Frequency
JP2021020028A	2021	JP	Temporomandibular	Rest	N. S	80 Hz
EP2432549A1 EP2432549A4	2012	EP	Knee	Rest or movement	Pad	N. S
US2016367798A1 US9757559B2	2016	US	Bone	Movement	Implant	N. S
AU2016202904A1	2016	AU	Ankle, back, arm, shoulder, wrist brace	Rest	N. S	100 Hz
CN113116679	2021	CN	Knee	Rest	N. S	N. S
CN209645158	2019	CN	Knee	Rest or movement	N. S	N. S
CN213466512	2021	CN	Knee and legs	Rest or movement	Electrode plate	N. S
CN105920738	2016	CN	Knee	Movement	Bag	N. S
US20180221658	2018	CN	Gluteus medius, biceps femoris, or gastrocnemius	Movement	N. S	40 to 200 Hz
CN203620081U	2014	CN	Multiarticular	Rest	N. S	N. S
US20200147378	2020	US	Knee	Rest	Electrodes	80 to 100 Hz
EP3328277A1 EP3328277A4	2018	EP	Knee	Rest or movement	N. S	10 to 200 Hz

For this reason, “JP2021020028 (A)” proposed a device for temporomandibular disorders (TMD), which provides an electrical signal to the masseter muscle or the trigeminal nerve using an electrode placed at or near the temporomandibular joint. It has a waveform generator unit of 80 Hz or more for the electrical signal output. Moreover, "EP2432549 (A1)" described a knee pad that includes a joint stabilization assembly unit

to relieve OA symptomatology. The electrostimulation unit was used in conjunction with the joint stabilization unit to provide a synergistic effect, which results in optimal knee joint treatment.

Also, “US2016367798 (A1)” suggested a dielectric implant, called Electret, to place the bone. After being stabilized in the bone, the electret implant reaches a certain magnitude, acting at the cellular level, becoming a catalyst for repaired processes in living tissues, and helping in the OA treatment. The invention “AU2016202904 (A1)” included support for the ankle, back, arm, shoulder, or wrist brace electric stimulation with a nominal frequency of 100 Hz. For the proper obtaining of positive results, the patient must use it for 150 hours during the treatment.

Beyond that, “CN113116679” provided a comprehensive treatment instrument for knee OA. The invention can fix the user's legs using a fixation device to perform passive exercise training, while the fixation device can rotate, performing stimulation through passive movement and electrical stimulation. In addition, “CN209645158” proposed a technical solution that comprises a thigh and calf rest connected by a hinge with a small low-frequency pulsed electrotherapy device.

Following the same strategy, "CN213466512" provided an electrode plate that promotes an efficient fixation for the user during outpatient activity. The device contained an electrode sheet used in the legs of a user and solved the problem of the electrode sheet falling off due to the movement of the legs of the user. The patent “CN105920738” configured a therapeutic bag for stabilization of the knee, with a central control panel and reservoir for the use of medication associated with stimulatory therapy.

Moreover, "US20180221658” provided a method of treating medial knee joint pain during gait in individuals affected by OA. The method comprises the application of functional electrical stimulation (FES) between 40 to 200 Hz in the gluteus medius, biceps femoris, or gastrocnemius during gait. The device stimulates and stabilizes the musculature during movement, proposing a correction of possible pelvic instabilities that lead to abnormal biomechanical compensation in the knee. Despite that, “CN203620081 (U)” described a device that involves microcurrents in a closed system, in which the output current from the energy source first passes through a circuit generating a positive

voltage across the first line of electrodes, then generates a negative voltage across an electrode opposite it.

“US20200147378” belonged to the TENS category, combining two sets of electrodes and a wireless and controllable portable signal generator applied in the path of the infrapatellar nerve, the first set vibrating at high frequency and the second at low frequency between 80 to 100 Hz, promoting the activation of different and complementary pathways in pain control. Then, “EP3328277 (A1)” developed a device used to gait retraining and modifying muscle activation patterns to treat knee pain associated with OA. The device is based on an electrical sensory stimulation and is configured to not induce contraction of a muscle since it has a low frequency beat between 10 to 200 Hz.

“CN109199670” developed an invention using acupuncture points combined with electrical stimulation to relieve pain and abnormal mechanical problems caused by knee OA. The device provides an electrical stimulation frequency of 2-100 Hz, an electrical stimulation wave width of 150-300 microseconds, and an electrical stimulation current intensity between 30 and 80 mus. "US289037034" related an electroacupuncture device implanted under a patient's skin surface corresponding to a patient's joint generating an electrical stimulation, with a frequency between 10 to 100 Hz. Lastly, “CN311659636” used the technology of electrical stimulation of the combined acupuncture points through a knee joint corrector, using a self-adhesive electrode sheet, which stimulate the acupuncture points.

Phototherapy

Phototherapy in modern era was used in 1903 for the first time, through an electric carbon arc torch to radiate ultraviolet light to lupus treatment. Nowadays, phototherapy is used in several diseases’ treatments, such as Alzheimer’s disease, Parkinson’s disease, rheumatoid arthritis, low back pain, and OA. Besides the effectiveness of this therapy, the parameters used to ensure the pain relief of the phototherapy still are unclear since the available studies have not established parameters and reported a range of outcomes [33,34]. However, phototherapy have been shown to reduce inflammation, induce analgesia, and promote healing of musculoskeletal disorders, which occurs through the increasing of nociceptive thresholds, resulting in pain

relief. Therefore, the phototherapy may be a valuable component in the management of OA [35].

In the present research, of the patents found directed to the OA treatment using phototherapy, some present different proposals for improving the use of these devices. As seen in **Table 2**, nine patents belong to this group of treatment. The "CN215309736U" invention discloses light support with a high-efficiency light source for multiarticular proposes, due to this the device enhanced self-service aid for deaf and mute professionals. Moreover, "CN212522734U" proposed a glove with an OLED light source, which has the advantages of high uniformity and low heat generation. For OA hand, due to the long treatment cycle, flexible OLED light can be used for home treatment without affecting normal life and work. The invention also has a sensor that can monitor the parameters required for phototherapy in real-time and provide a basis for adjusting of light intensity.

Table 2. Main patents that describe Phototerapy devices.

Publication Number	Year	Country	Priority articulation	Rest/Movement Use	Device	Ligh Source
CN215309736U	2021	CN	Multiarticular	Rest or movement	Support	High-efficiency light source
CN212522734U	2021	CN	Fist or hand	Rest or movement	Glove	OLED light
CN209107989U	2019	CN	Knee	Movement	Bed	Infrared radiation
CN83934919	2010	CN	Cervical, lumbar/ cervical vertebra	N. S	Belt	Far infrared rays
CN110917506A CN110917506B	2020	CN	Knee	Movement	Knee brace	Blue infrared laser
CN113679956A	2021	CN	Knee and elbow	Rest or movement	Chair	Infrared technology
CN210963591U	2020	CN	Fingers	Rest	Robot	Infrared lamp
CN213695775U	2021	CN	Knee	Movement	Pad	Far infrared layer
CN214105148	2021	CN	Leg	Rest	muscle maintenance device	Light irradiation lamps

Moreover, the utility model of the patent "CN209107989U" is a bed with infrared radiation destined for the treatment of knee OA. The device guarantees a safe

and effective rehabilitation of the knee joint since it provokes the improvement of joint inflammation, prevents joint adhesion and activity range from being affected, and increases blood and lymph circulation. “CN83934919” also proposed a belt with infrared radiation technology, in this case, the device is directed to the cervical and lumbar OA. The phototherapy belt has the effects of activating blood and dissolving stasis, freeing channels and quickening network vessels, and dispersing swellings and relieving pain. It has a quick response, good effect and low recurrence rate of OA. Infrared light is a type of electromagnetic radiation with wavelengths, shorter than microwave radiation and longer than visible light, which derives from thermal energy[36].

Furthermore, “CN110917506 (A)” used a knee pad. However, in this case, the invention had a blue infrared laser, and the treatment can be carried out while moving since the knee movement helps the laser beam's ability to reach the specific point in motion. The invention “CN113679956 (A)” discussed a medical rehabilitation chair for joints, using infrared technology, focusing on the knee and elbow. The treatment occurred through strips of infrared lamps present in the device.

Beyond that, high technology has been developed, such as “CN210963591 (U)” which described as an OA rehabilitation device that helps patients exercise their fingers. The invention is a robot developed to perform the mechanism of flexion, rotation of the finger root, and anti-compression. Moreover, the device used an infrared lamp and control system for these activities. Benefiting from device for OA rehabilitation is an intelligent strategy since it provides movements that assist the patient in movement with their own voluntary impulse, making the patient active in the process [37].

“CN213695775 (U)” developed a knee pad, with far infrared layer technology, which can lead to reduced swelling and inflammation in the knee joint to relieve pain through the heat integration. “CN214105148” proposed a leg muscle maintenance device composed of light irradiation lamps.

Infrared radiation can be developed with luminous or non-luminous lamps. The therapy depends on the lamp’s intensity, which needs to be placed at a distance between 45 and 75 cm from the patient’s body. Exposure should be limited to 10-15 minutes, and eye coverage is recommended [36,38]. Therefore, due to the low energy intensity and wavelengths, phototherapy is capable of penetratingbiological tissues and can influence the synthesis, release and metabolism of numerous signaling substances involved in analgesia [39,40].

Ultrasonic Therapy

Ultrasound (US) is a modality of longitudinal sound energy with deep penetration, which, when transmitted to biological tissues, can produce cellular changes through mechanical effects1. Its therapeutic application predates its use as an imaging technique. The US first appeared as physical therapy for European football players in the 1920s [41]. Produced by an alternating current flowing through a piezoelectric crystal housed in a transducer that generates sound energy, therapeutic ultrasound (TUS) is a resource widely used in clinical practice [42].

The effects of TUS can be divided into thermal and non-thermal. The frequency of the transducer can be 3 MHz, more superficial, with a depth of 1 to 2 cm, or 1 MHz, which reaches deeper tissues from 3 to 5 cm [43]. TUS intensity can vary between 0.1 and 0.3 W/cm2 and, recently, some device has been redesigned to present intensity limits more compatible with clinical practice, ranging from 0.1 to 2.0 W/cm^2. Several methods are available for the application of TU, including direct or sliding, underwater, balloon, reflector, funnel, reflex paravertebral, and head reducer (**Table 3**) [44].

Table 3. Main patents that describe Ultrasonic Therapy devices

Publication Number	Year	Country	Priority articulation	Rest/Movement Use	Device	Ultrasound Wave
KR102115395B1 KR20200052533A	2020	KR	Knee	Movement	Band	N. S
KR20210158487A	2021	KR	Multiarticular	Rest	N. S	up to 30 MHz
KR102054002B1	2019	KR	Multiarticular	Rest	Cushion	0.2 to 1.0Mhz
KR101396285B1 KR20140028894A	2014	KR	Multiarticular	Rest	Ultrassonic plate	4000 to 4100 Hz
KR20200052538A	2020	KR	Multiarticular	Rest	Belt	N. S
CN210674031U	2020	CN	Knee	Rest	Head positioner	N. S
KR20190123190A	2019	KR	Lower members	Movement or rest	Cushion	0.5 to 3 MHz

Of the seven selected patents, some present different proposals to improve the effectiveness of ultrasonic waves. The invention “KR102115395 (B1)” proposed a band that allows the involvement of the entire knee joint, increasing penetration efficiency, minimizing the contact of ultrasonic waves with the air, and concentrating the conductive gel at the site desired, promoting better adherence to the skin and consequently increasing the effectiveness of the treatment. TU can reduce pain, increase perfusion, decrease joint stiffness, and enhance collagen extensibility and tissue healing [45].

“KR20210158487 (A)” allows the user to recognize the operation of ultrasonic waves, considering that they vibrate in a sound range inaudible to humans. The device has two vibration units operating concurrently, one sonic and the other ultrasonic. Furthermore, the invention generates a control signal for oscillation up to 30 MHz and a vibration signal for 16 Hz to 1 MHz. Moreover, “KR102054002 (B1)” developed a multi-joint cushion adaptable to the joint structure. In this device, the US focused on transmitting ultrasonic waves in the cartilage between the joints and varying the distance between the plurality of ultrasound. In this device, the user can adjust the frequency intensity of the ultrasonic wave in the range of 0.2 to 1.0Mhz. The treatment time can also be adjusted between 5 and 30 minutes.

“KR101396285 (B1)” referred to a low-intensity US device that uses history according to the patient's age, body shape, location of body application, arthritis type, duty cycle, and pulse width. The device can be used in different individuals regarding the parameters in a safe and individualized way, maximizing their therapeutic effects. The invention presents medium frequency waves from 4000 to 4100 Hz to penetrate the deep portion of the skin without resistance, thus reducing muscle spasms and controlling pain. The invention “KR20200052538 (A)” described a multi-articular, stable and adaptable belt to treat only the cartilaginous region, reducing friction and exposure of the bone region to ultrasonic waves.

Beyond that, “CN210674031U” described a utility model made of latex and plastic as an auxiliary treatment for ultrasonic devices. It is a joint positioner that seeks to improve the positioning accuracy of the US head, thus obtaining a better therapeutic effect. One of the preponderant characteristics of the pathophysiology of OA is

inadequate bone growth, resulting in a joint with multiple deformities, which prevents the desired therapeutic effect due to the dispersion of sound waves through the joint slopes.

Lastly, “KR20190123190 (A)” developed a portable ultrasonic therapy product to act on lower limb muscle strengthening and OA pain relief. This invention has an ultrasonic pad with a wavelength of 0.5 to 3 MHz at a low frequency, increasing local tissue temperature. This mechanism provides a synergistic effect to suppress cartilage tissue degeneration and treat pain. In addition, because it is portable, this device can be applied at rest or in movement. It exercises and drives muscle strengthening, through this mechanical technique is feasible.

Therefore, current results point to TUS as an appropriate technique for pain control and functionality in OA. However, TUS is not significant when associated with other procedures, such as kinesiotherapy and neuromuscular electrostimulation, since several factors interfere in maximizing the therapeutic effects of TUS, such as contact area and parameters used application method [46].

Magnetotherapy

Magnetotherapy is an alternative and adjuvant treatment used in physical therapy to rehabilitate musculoskeletal injuries. In different parts of the word, people know that some natural materials possess magnetic properties and might be used for healing and treating some health issues. The magnetotherapy used nowadays began in Japan, after World War II, and passing to Europe, whereas the therapy received attention fromresearch due to its effects. Over 25 years, this therapy has been used for bone unification in delayed fractures. Thus, magnetotherapy has amechanism of action based on the deeppenetration in the tissue, modulating molecular and cellular functions [47– 49].

For this reason, four patents were selected for this group, as shown in **Table 4**. “CN108836781(A)” and “CN109045473(A)” described a massage device to treat knee OA through magnetic therapy with automatic adjustment of the position of the knee. Therapeutical massage is the manipulation of the soft tissue of whole-body areas to improve health, such as relaxation and relief of muscular aches and pains. Therefore, the soft-tissue massage promotes the relief of pain based on the release of endorphins as well

as the stimulation of large diameter nerve fibers, which depresses the T-cell activity, followed by the pain relief [50].

Table 4. Main patents that describe Magnetotherapy devices.

Publication Number	Year	Country	Priority articulation	Rest/Movement Use	Device	Innovation
CN108836781A CN108836781B	2018	CN	Knee	Rest	N. S	Massage
CN109045473A	2018	CN	Knee	Movement	Support	Massage
CN211268741U	2020	CN	Knee	Rest or movement	Knee pad	Bio-energy magnets
CN110917501A CN110917501B	2020	CN	Multiarticular	Rest or movement	Plate	Magnetic suction

Moreover, "CN211268741 (U)" proposed a magnetotherapy pad, which solves the problem of pain on the inside or outside of the patient's knee joint due to knee inversion or valgus. The device can relieve the pain trough the massage along with bio-energy magnets. Another technique has been used to propose the improvement of OA, using infrapatellar fat pad. This device is located intra-articularly andextrasynovially in the knee joint and present an abundance in adipose tissue [51].

Magnetotherapy can penetrate deeply into the skin, being effectively influence in normal and injury currents since the energy applied is below the thermal threshold level. Moreover, this therapy is less expensive, comfortable and easier to apply, without complications of contact electrodes since the contact is not necessary to achieve the desired management at tissue level [48]. For this reason, "CN110917501 (A)" described a magnetic suction plate for multiarticular targets, which can fit each other at the joints, and adjusting the position after fixation without disassembly.

Electromagnetic Therapy

Electromagnetic fields (EMFs) have shown positive effects on OA treatment and other bone disorders, such as fresh fractures, delayed and nonunion fractures. Beyond that,EMF therapy has rapid effect, ease of operation, and lack of adverse effects, which is suitable for widespread application [52]. Despite the advantages, EMF action

mechanism is still unclear at present; due to these electromagnetic therapies are still not generally accepted in all the countries as "standard treatment" and can be used as adjuvant therapy [48,53]. The frequencies used in this therapy is at the lower end of the electromagnetic spectrum, between six to 500 Hz, but can also feature short wave frequencies [54]. Beyond the frequencies, the treatment period, waveform, and amplitude differences in EMF result in different outcomes [55]. According to **Table 5**, five patents presented the EMFs therapy in their invention.

Table 5. Main patents that describe Electromagnetic Therapy devices.

Publication Number	Year	Country	Priority articulation	Rest/Movement Use	Device	Eletromagnetic Field
CN217903667	2018	CN	Knee	Rest	N. S	LFPEMF (0 to 300Hz)
CN196171455	2017	CN	Knee	Rest	N. S	LFPEMF (0 to 300Hz)
CN202603679U	2012	CN	Knee	Rest	Brace	LFPEMF
CN234781605	2018	CN	Knee	Rest	N. S	Ultra-short electromagnetic waves
CN311654821	2020	CN	Knee	Rest	N. S	Microwave technology

Therefore, "CN217903667" and "CN196171455" developed a low-frequency pulse electromagnetic field (LFPEMF) and system for treating knee OA and cartilage injury with a wave current frequency adjusted between zero and 300 Hz. In this same scenario, "CN202603679 (U)" proposed a knee pad, which has the technology LFPEMF. The invention relieves knee muscle and nerve pain, which promotes blood circulation, and achieves knee OA treatment functions. However, LFPEMF currently used in the treatment of knee OA has not been fully developed. In the current market, the magnetic therapeutic apparatus for treating knee OA mainly utilizes electrical stimulation to cooperate with a static magnetic field [56].

Beyond that, "CN234781605" reported a device fitted for skillful correction of knee OA. In addition to monitoring the knee joint and changes in the range of motion of the affected limb. Because of these functions, it perceives and corrects the internal and external pressure and load and, through ultra-short electromagnetic waves, in the middle of the thigh support, eliminates internal inflammation and corrects the deformity. Moreover, "CN311654821" developed a rehabilitation training device for knee OA,

through microwave technology, to promote microcirculation in the region and absorption of necrotic substances, as well as the recovery and rehabilitation of the patient.

Thermotherapy

Thermotherapy is a more than 2,000-year-old technique that consists of applying heat to a region of the body, generating an increase in temperature that helps to relax the muscles and enhance circulation to the affected area, reducing pain and stiffness [57–61]. Among the thermotherapy techniques are the application of moxibustion, superficial heat, hot compresses and via diathermy, application of electromagnetic energy. Treatment can be easily self-applied by the patient and can be applied together with other rehabilitation interventions [61]. Thermotherapy was identified in two patents in this review, as shown in Table 6.

Table 6. Main patents that describe Thermotherapy devices

Publication Number	Year	Country	Priority articulation	Rest/Movement Use	Device	Temperature
CN293771361	2020	CN	Knee	Rest	Pad	70°C
CN203564513U	2014	CN	Knee	Rest	Cap	N. S

For this reason, “CN293771361” described a knee pad that used thermotherapy at a temperature of 70°C, associated with acupuncture, proposing a simple and cheap treatment. The invention can be used as homecare, optimizing the improvement process and generating a better quality of life. Following the same principle of thermotherapy, "CN203564513U" developed a device that is composed of an inner ceramic cylinder, a temperature controller and a power plug, which can have multiarticular use. Therefore, this technology is promising since its easy, has non-invasive application and has few adverse events [61].

The small number of patents can be explained by the inconclusive results of studies on the effectiveness of thermotherapy in the treatment of OA (**Table 6**) [61]. Beyond that, cold causes vasoconstriction, which results in stimulation of the smooth muscle of blood vessels reducing the release and production of histamine and prostaglandin, causing a reduction in chemical mediators associated with inflammation

[62–69]. On the other hand, heat increases blood flow through vasodilation, muscle contraction velocity, capillary permeability, and nerve conduction, generating most of the time the reduction of pain in patients with OA [69–71].

Associated Therapies

Non-pharmacological management has been an emphasis in the OA treatment since the approaches can be adapted to the individual patient. Orthoses, pads, sticks, and other assistive devices are mainly prescribed and recommended to modulate mechanical stress on the symptomatic joint compartment [72,73]. However, no therapies have been able to halt or delay OA progression or provided effective and long-lasting symptomatic relief. Novel therapeutic approaches used to decrease the OA degenerative and inflammatory process in cartilage requires a deep understanding of the disease level[74]. Therefore, the association of therapeutic techniques can bring numerous benefits to OA therapy since presented 12 patents (**Table 7**).

Table 7. Main patents that describe Associated Therapies devices

Publication Number	Year	Country	Priority articulation	Rest/Movement Use	Device	Innovation
Electromagnetic Therapy and Thermotherapy						
US20220008741	2022	US	Neck, knee, back, hand and wrist	Rest	N. S	PEMF (60 Hz)/39 to 42°C
CN108607161A CN108607161B	2018	CN	Knee and lumbar spine	Rest	Magnetic tape	Magnetic correction/40 to 50 °C
CN202603679U	2012	CN	Knee	N. S	Pad	LFPEMF
CN205548791U	2016	CN	Multiarticular	Rest	Belt	Electromagnet column and heat-conducting layers
Electrotherapy and Phototherapy						
CN208626444U	2019	CN	Knee	Rest	Smart pad	Infrared technology with electrode currents
CN205612882U	2016	CN	Knee	Rest	N. S	Small portable electrode type infrared blue laser
Electrotherapy, Thermotherapy and Electromagnetic Therapy						

CN107811747A	2018	CN	Multiarticular	Rest	N. S	Electric heating warmer and an electromagnet
CN202603679U	2012	CN	Knee	Rest	Pad	Low-frequency pulse
Ultrasound and Phototherapy						
CN107811747A	2021	CN	Multiarticular	Rest	Ceramics	Infrared ceramic and US waves (0.5 to 1.5 MHz)
KR102297628B1 KR20210027587A	2021	KR	Multiarticular	Rest	Ceramics	Far-infrared ceramic and US
Ultrasound and Electrotherapy						
CN208611613U	2019	CN	Head	Rest	Annular structure	TENS and US (0.6 MHz)
CN109998484A CN109998484B	2019	CN	Multiarticular	Rest	Head positioner	Laser and US

Electromagnetic Therapy and Thermotherapy

"US20220008741" proposed a thermally assisted pulsed electromagnetic field therapy (PEMF) to treat systems of various body parts, such as neck, knee, back, hand and wrist. PEMF used a frequency of 60 Hz and a stabilizing temperature of 39 to 42 C°. "CN108607161 (A)" related a magnetic correction and stability, after the pain localization, massage, and hot compress in knee and lumbar spine. The process should be repeated in two or four weeks to complete the treatment and achieve the pain relieve. The hot compress step had a temperature stablished of 40 to 50°C, and heat for 20-30 minutes. Also, the magnetic correction and stability occurred during 40 to 60 minutes and 8 to 10 hours, respectively.

Moreover, "CN202603679 (U)" proposed a knee pad, which has the technology of electromagnetic therapy, through the LFPEMF and a heating element, such as a positive temperature coefficient (PTC) thermistor. Thus, the device relieves knee muscle and nerve pain, promote blood circulation, achieve knee OA treatment functions. "CN205548791U" designed a device that comprises a heat generator associated with a massager structure and an electromagnet column. The device has belts, stabilization tapes,

heat-conducting layers, and coils for transducing the massager structure and therapeutic electromagnetic stimulation, enabling positive recovery for the region to be treated.

Electrotherapy and Phototherapy

"CN208626444 (U)" and "CN205612882 (U)" proposed devices that combine the technique of electrotherapy with phototherapy through infrared technology to treat knee OA. Both devices have their application aimed at increasing the chance of local knee joint regeneration and analgesia, which promotes the reduction of nerve excitability and improvement in blood flow. As for the employability of electromagnetic therapy, the patent suggests that electrode currents penetrate the skin and improve circulation.

Electrotherapy, Thermotherapy and Electromagnetic Therapy

"CN107811747 (A)" developed an electric heater to heat the joints, relieving pain, which achieves uniform heating. The invention works through a control device connected to the pressure sensor and an electromagnet. "CN202603679 (U)" proposed a knee pad, which has the technology of electrotherapy therapy, low-frequency pulse, and thermal therapy. The invention relieves knee muscle and nerve pain. Also, the device promotes blood circulation and achieves knee OA treatment functions. Because of this, electrotherapy and thermotherapy have been used as part of a rehabilitation program for various musculoskeletal conditions, thus helping to relieve pain, inflammation, and stiffness. It may indirectly contribute to the increase in muscle strength and mobility [75].

Ultrasound and Phototherapy

"CN112439132 (A)" and "KR102297628 (B1)" approached infrared using infrared ceramic applied phototherapy and US techniques, with similarity in the frequency range of 0.5 to 1.5 MHz. This combination of methods focuses on the treatment of bone tissue damaged because of OA. Therefore, this ceramic system emits far infrared rays that increase the volume and reduction of transverse bone segments and enhance the pain threshold and thus controlling pain. Furthermore, US raises the intracellular concentration of calcium (Ca^{2+}) and its vibrations transmitted in the cartilaginous tissue induce activation of chondrocytes[76,77].

Ultrasound and Electrotherapy

"CN208611613 (U)" took advantage of electrotherapy and ultrasound to treat the inflammatory process of OA and the correlated damages with the TENS. Therefore, to increase the depth of the wave range, the frequency used was 0.6 MHz, already to reduce the discomfort of the treatment and introduce the TENS aspect.

An early and accurate diagnosis is necessary and important to control the progression of OA. “CN109998484 (A)” used electrotherapy and UST. The device recognizes the degree of the disease and specificity to discern synovitis from OA, evaluating hyperemia and hypoxia. The patent suggested that by combining the two techniques, the device provides precise localization of damaged cartilage and targeted laser and ultrasound treatment.

Other Therapies

As seen in **Table 8**, other therapies, which were not described above, were also found, establishing a total of two patents. “CN205512471 (U)” is a knee brace that uses negative ions to neutralize free radicals and consequently reduce symptoms. In addition, these ions can increase calcium concentration generating nerve conduction to reduce pain. Iontophoresis reaches deeper tissues through the skin or mucosa, ensuring strong analgesic, anti-inflammatory, and anti-swelling effects. However, several factors influence the effectiveness of iontophoresis treatment, such as particle size and charge, intensity and type of the current flow, the duration of the procedure, and the device used in the treatment [78].

Table 8. Main patents that describe other therapies devices.

Publication Number	Year	Country	Priority articulation	Rest/Movement Use	Device	Therapy
CN205512471U	2016	CN	Knee	Rest or movement	Brace	Ion therapy
CN311654821	2020	CN	Knee	N. S	N. S	Microwave

CONCLUSION

Patent prospecting has shown essential importance since it is through it that can be identified the growing innovations present in the market and future initiatives for the development of other technologies. Within the field of physical therapy, this type of study is new, current, and of extreme interest to researchers in this area. Due to the patent market determinant factor, it was identified in this review that there are new technologies for symptom management, especially pain, in OA. However, these innovations have not yet reached the daily lives of patients affected by this disease. To understand the global situation of the devices already developed for this disease treatment, this is the first article that aims to prospect patents for physical therapy devices. The therapeutic fields that

presented the most documents were electrical stimulation, phototherapy, and ultrasound, followed by magnetic, electromagnetic, and thermotherapy. From this perspective, it can be observed that the most current therapies are already on the market. In this context, the needing to develop new technologies for managing OA symptoms is still current, and this article presents itself as a basis for this action.

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4 DISCUSSÃO GERAL

Dentro do sistema primário de saúde, a OA está presente entre as doenças mais comuns (EBELL, 2018). Devido a sua cronicidade e fatores degenerativos da cartilagem, a OA acomete principalmente idosos, podendo ocorrer em qualquer articulação, mas é observada, majoritariamente, em grandes articulações das extremidades inferiores, como quadril e joelho. Essas articulações são responsáveis pelas atividades de carga, absorvendo as vibrações e impactos dos movimentos cotidianos. Portanto, quando em casos avançados, a OA pode diminuir e prejudicar a qualidade de vida do paciente (TSOKANOS et al., 2021).

Apesar dos prejuízos atrelados ao paciente acometido pela OA, esta doença ainda não tem cura. Os tratamentos presentes no mercado são baseados apenas no manejo dos sintomas que a OA apresente, principalmente em relação à dor crônica. Sendo assim, a busca de novas alternativas para a melhoria da qualidade de vida desses pacientes é alvo constante por parte dos pesquisadores. Devido aos acontecimentos atuais de ordem mundial, como a pandemia do novo coronavírus (COVID-19), diminuíram os investimentos em desenvolvimento e pesquisa, ou até mesmo em relação ao uso de medicamentos (KARASAVVIDIS et al., 2020).

Ainda que haja uma redução do foco de pesquisas na área ortopédica, o mercado terapêutico para a OA está projeto para atingir 11 bilhões de dólares em 2025. Estes números refletem a presença de uma grande população de pacientes geriátricos (MARKETS AND MARKETS, 2020). Sendo assim, o primeiro capítulo da dissertação refere-se ao artigo submetido na revista *Critical Reviews in Therapeutic Drug Carrier Systems* intitulado *The management of osteoarthritis symptomatology through nanotechnology: a patent review* que aborda as principais terapias com foco na nanotecnologia protegidas por patentes para o tratamento da OA.

Em razão da necessidade de alternativas para o manejo da OA, atrelado ao período de sigilo de 18 meses que os pedidos de patentes passam após pedido de proteção da invenção, foram selecionados 16 documentos que propõem inovações nesse campo. Dentre as patentes analisadas, houve um crescimento do número de publicações a partir do ano de 2016, que provavelmente deve-se ao chamado da *Osteoarthritis Research Society International* para a causa em 2015, trazendo um foco maior para a doença e o desenvolvimento de novas tecnologias. Ademais, países asiáticos e desenvolvidos foram os principais depositantes de invenções terapêuticas, como a China, República da Coréia e Estados Unidos da América. Além de contar com a forte presença das universidades como os principais investidores dessas invenções.

Em relação as terapias analisadas, três categorias de vias de administração foram encontradas: intra-articular, oral e tópica. A via intra-articular foi a mais presente nas patentes selecionadas, uma vez que esta via representa uma gama de possibilidades de formulação, pois apresenta uma rápida depuração dos fármacos após a administração. Portanto, quando o tratamento é diretamente injetado na articulação, apenas um pequeno volume de fármaco é necessário para exercer a atividade farmacológica desejada e diminuir a exposição do fármaco a locais inapropriados (ABRAMSON, 2006).

Quando associada à um sistema apropriado de liberação, como as nanopartículas, pode intensificar o aumento da dose local de fármacos e prolongar sua retenção na cavidade articular (CHEN et al., 2021). Nesse contexto, as nanopartículas foram as principais nanotecnologias associadas à via intra-articular, uma vez que pequenas partículas são facilmente injetadas, mas rapidamente eliminadas através de fenestrações da membrana sinovial das articulações, que variam de nanômetros a vários micrômetros de tamanho (PRADAL et al., 2016).

Outro aspecto observado foi o uso de polímeros na produção das inovações nanotecnológicas, principalmente a polivinilpirrolidona (PVP), poli (ácido Iáctico-co-glicólico) (PLGA) e polietilenoglicol (PEG). Essa alternativa tornou possível grandes avanços em aplicações de sistemas de liberação de fármacos, uma vez que os polímeros funcionais podem ser usados para o encapsulamento de agentes terapêuticos melhorando as características físico-químicas dos fármacos, bem como a sua atividade biológica (FARJADIAN et al., 2019). Desta forma, NPs de PLGA, por exemplo, são internalizadas nas células por pinocitose e endocitose, escapam rapidamente dos endolisossomos e entram no citoplasma, o que facilita as interações das NPs com as membranas vesiculares. Além disso, polímeros como o PLGA foram aprovados pelo FDA em diversas formulações, devido ao seu alto desempenho (DANHIER et al., 2012).

Os tratamentos para OA presentes no mercado são limitados e a maioria destes apresentam como foco o alívio da dor. Em contrapartida, as patentes selecionadas propuseram inovações que podem interferir na progressão da doença. Sendo assim, as formulações foram baseadas em terapias através do antagonismo da apoptose de condrócitos e promovendo o crescimento celular, redução do nível de citocinas inflamatórias no fluido articular, ou até mesmo por meio de fatores de diferenciação da cartilagem (LIU et al., 2014; PENG et al., 2020; KHANG et al., 2020).

No entanto, o uso da nanotecnologia no tratamento da OA, em casos mais avançados, não é o bastante, fazendo necessário a união desse tipo de terapia com outras abordagens, como as não-farmacológicas. Nesse contexto, o segundo capítulo da dissertação corresponde ao artigo

a ser submetido na Journal of Science: Advanced Materials and Devices intitulado Technological prospection of non-pharmacological devices for the treatment of osteoarthritis symptoms through patent review, que discutiu sobre os principais aparelhos relacionados ao manejo dos sintomas da OA.

As principais abordagens encontradas na revisão consistiram em: estimulação elétrica terapêutica, fototerapia, terapia ultrassônica, magnetoterapia, terapia eletromagnética, termoterapia e terapias associadas. Ao total 57 documentos de patentes foram selecionados do período de 2010 a 2022 no que se refere a aparelhos e dispositivos que proporcionem melhorias na qualidade de vida dos pacientes acometidos por OA. Os modelos de utilidades encontrados buscam trazer novas alternativas e solucionar problemas referente a tempo de tratamento, potencialidade do dispositivo, aumento da mobilidade do paciente, praticidade e eficácia da terapia, comparados àqueles que já existem no mercado.

A triagem das patentes selecionadas identificou 15 documentos no ano de 2020, apresentando o maior número de publicações. Em relação aos países aplicantes, a China aparece novamente como detentor de 38 patentes e a indústria e companhias farmacêuticas em parceria ou não com inventores independentes e universidades como os principais investidores dessas invenções. Além disso, em patentes que tratavam de uma única articulação, o joelho foi o principal foco de pesquisas.

A estimulação elétrica terapêutica foi alvo de 12 patentes, as quais buscaram variar nos dispositivos e no pulso elétrico utilizado na terapia. Este variou entre 10 e 200 Hz, o que consolida o maior uso da terapia elétrica de alta frequência (VANCE et al., 2014). A fototerapia foi o segundo maior destaque, apresentando nove documentos. Estas patentes utilizaram fontes de luz para o tratamento da OA, principalmente luzes ao nível infravermelho, as quais procuraram obter inovações mais flexíveis, além do estabelecimento dos parâmetros necessários para fornecer uma terapia eficaz e ajustar a intensidade da luz (VADER et al., 2020).

Os efeitos das modalidades físicas no ambiente articular, bem como suas implicações clínicas nos estágios iniciais da OA, ainda são pouco conhecidos (ABRAMOFF; CALDERA, 2020). Embora, haja uma enorme variedade de agentes físicos disponíveis, sua aplicabilidade na prática clínica gera dissonâncias quanto aos reais benefícios em relação a utilização individualizada dessas terapêuticas, sendo fundamental o estudo dos efeitos dessas intervenções não apenas no controle da dor, mas também em quaisquer alterações induzidas no tecido articular, como a cartilagem articular e o osso subcondral, afetados diretamente na fisiopatologia da OA (GÜVEN, 2021).

Apesar disto, o uso desses agentes é apoiado por alguns estudos com limitações metodológicas, principalmente nas informações de dosagem e seus efeitos geralmente baseados apenas no alívio da dor em curto prazo. Tal condição limita a busca por estratégias e desenvolvimento de terapêuticas, produtos e mecanismos mais eficazes no combate a OA, e ainda influência de forma negativa as tomadas de decisões assertivas na prática clínica, gerando diversos vieses metodológicos e limitando o avanço apropriado para a cura desta doença (BROSSEAU et al., 2014; MCALINDON et al., 2014; RANNOU; POIRAUDEAU, 2010).

5 CONCLUSÃO GERAL

As prospecções de patentes quando realizadas permitem a detecção de tecnologias já existentes, o seu grau de maturidade, além de servir de auxílio para mapear alternativas terapêuticas para tratamento, prevenção e cura de inúmeras patologias. Através do presente mapeamento de patentes realizado pode-se encontrar informações tecnológicas a respeito de importantes abordagens frente ao tratamento da osteoartrose.

A primeira revisão de patentes realizada discutiu sobre o desenvolvimento de inovações, estratégias e alternativas terapêuticas utilizando a nanotecnologia no tratamento da osteartrose. Os achados encontrados apontaram tratamentos focados nas vias intraarticular, oral e tópica, sendo que os melhores resultados convergiram para os métodos intra-articulares. Entretanto, a via oral, que ainda hoje, é a mais utilizada, continua sendo a mais rápida e eficaz, principalmente no alívio da dor e desconfortos decorrentes desta patologia. Logo, o desenvolvimento de novas tecnologias, como a nanotecnologia, permite vislumbrar um futuro promissor e positivo no tratamento da OA.

A segunda revisão abordou o rastreio de tratamentos não farmacológicos envolvendo terapias associadas a dispositivos fisioterapêuticos. As patentes mapeadas tiveram como mecanismo de ação agentes físicos, tais como a eletroterapia, termoterapia, fototerapia, terapia eletromagnética, ultrassom terapêutico e magnetoterapia. Entretanto, o déficit de informações específicas sobre parâmetros utilizados, conteúdo e modo de entrega de cada mecanismo torna-se um grande viés na escolha de estratégias mais precisas e eficazes para o tratamento da OA.

Logo, entende-se a necessidade da continuidade do desenvolvimento de novas tecnologias que tragam uma luz para futuro da OA em termos de prevenção efetiva e cura da patologia, já que até o momento os tratamentos, tanto farmacológicos quanto não farmacológicos, disponibilizados no mercado mundial, referem-se ao manejo da sintomatologia da doença. Além disso, vale ressaltar a necessidade de trabalhos mais seguros e informações mais assertivas e detalhadas referentes aos dispositivos já existentes possibilitando tomadas de

decisões mais eficazes, precisas, seguras e menos impactantes aos indivíduos acometidos, já que a OA é uma patologia de ordem crônica e degenerativa.

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