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FITOTERÁPICOS DE USO ORAL COMERCIALIZADOS NO BRASIL PARA O TRATAMENTO DA OSTEOARTRITE: REVISÃO SISTEMÁTICA E METANÁLISE

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Orientadora: Profa. Dra. Cristiane de Cássia Bergamaschi

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A Deus, por ser essencial. Seu fôlego de vida me dá coragem para propor sempre um novo mundo de possibilidades.

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“Às vezes ouço passar o vento; e só de ouvir o vento passar, vale a pena ter nascido.”

(Fernando Pessoa)

RESUMO

A osteoartrite (OA) afeta 1% da população mundial e é a causa mais comum de incapacidade músculo-esquelética em idosos. Medicamentos à base de plantas medicinais são comumente comercializados e usados pela população brasileira para controlar os sintomas associados à OA. O objetivo deste estudo foi avaliar a efetividade e a segurança de 13 medicamentos à base de plantas comercializados no Brasil para o tratamento da OA. Trata-se de uma revisão sistemática e metanálise de ensaios clínicos controlados randomizados em pacientes adultos com OA de joelho e/ou quadril tratados com fitoterápicos das plantas: *Harpagophytum procumbens*, *Uncaria tomentosa*, *Salix alba* (ambos financiados pelo governo brasileiro), *Curcuma longa* (ou *Curcuma domestica*), *Chenopodium ambrosioides, Cordia curassavica* (ou *Cordia verbenacea*), *Zingiber officinale*, *Persea gratissima* (ou *Persea americana*) (pertencem a Relação Nacional de Plantas Medicinais de Interesse ao Sistema Único de Saúde), *Boswellia serrata*, *Bowdichia virgilioides*, *Salix daphnoides, Salix purpurea* e *Uncaria guianensis*, em comparação com placebo ou controles ativos. A busca por estudos elegíveis foi realizada nas bases de dados eletrônicas: *CENTRAL*; *MEDLINE*; *EMBASE*; *CINAHL*; *Web of Science*; *Health Star*; *AMED*, *the database of the Cochrane Complementary Medicine Field*, *LILACS*; *CAB abstracts*, *clinical trial.gov*, *WHO Trial Register* e Banco Nacional de teses da CAPES. Foram combinados os termos que descrevem OA e as plantas medicinais, individualmente. Foram medidos os desfechos primários: dor, função física, rigidez, edema, qualidade de vida e os desfechos secundários: eventos adversos, número de pacientes que relataram eventos adversos, satisfação com o tratamento, consumo de medimento de resgate e mudança na estrutura da articulação. De 2.241 estudos encontrados, 16 foram incluídos na revisão sistemática, e destes, nove foram incluídos na metanálise. Apenas três estudos preencheram todos os critérios de análise crítica e apresentaram risco mínimo de viés. *H. procumbens* teve eficácia semelhante à diacereína, apresentou melhor perfil de segurança e usou menos medicamento de resgate. *B. serrata* foi mais eficaz para dor e função física, e foi considerada mais segura comparada ao placebo e ao valdecoxibe. Os resultados da metanálise não comprovaram o benefício da *U. guianensis* em relação ao placebo para reduzir a dor; e nem da *S. purpurea* e *S. daphnoides* em relação ao placebo e ao diclofenaco para redução da dor, embora tenham se mostrados seguros. *C. longa* não foi superior ao ibuprofeno para a redução da dor e melhora da função física, mas foi considerada mais segura. *Z. officinalle* mostrou ser mais eficaz que placebo na redução da dor, e apresentou perfil de segurança semelhante ao diclofenaco e placebo. Os resultados deste estudo devem ser vistos com cautela devido ao baixo número de estudos incluídos. As evidências não foram suficientes para afirmar a efetividade e segurança destes fitoterápicos para AO. Desta forma, este estudo orienta os gestores do sistema de saúde pública e prescritores na tomada de decisão quanto ao uso destes fitoterápicos para OA.

Palavras-chave: Osteoartrite, Plantas medicinais, Efetividade, Segurança.

ABSTRACT

Osteoarthritis (OA) affects 1% of the world population and is the most common cause of musculoskeletal impairment in the elderly. Herbal medicines are commonly used in Brazil to control the symptoms associated with OA, however, the effectiveness of most of these agents is still unclear. The aim of this study was to evaluate the efficacy and safety of 13 herbal medicines sold in Brazil for the treatment of OA. This is a systematic review and meta-analysis of randomized controlled trials in adult patients with knee OA and/or hip treated with herbal plants: *Harpagophytum procumbens*, *Uncaria tomentosa*, *Salix alba* (financed by government), *Curcuma longa* (or *Curcuma domestica*), *Chenopodium ambrosioides*, *Cordia curassavica* (or *Cordia verbenacea*), *Zingiber officinale*, *Persea gratissima* (or Persea americana) (they are in the National List of Medicinal Plants of Interest to the Unified Health System) *Boswellia serrata*, *Bowdichia virgilioides*, *Salix daphnoides, Salix purpurea* and *Uncaria guianensis* compared with placebo or active controls. The search for eligible studies was conducted in electronic databases: CENTRAL; MEDLINE; EMBASE; CINAHL; Web of Science; Health Star; AMED, the database of the Cochrane Complementary Medicine Field, LILACS; CAB abstracts, clinical trial.gov, WHO Trial Register and Brazilian database of Theses of CAPES. The terms that describe OA and medicinal plants were combined, individually. Primary outcomes were measured: pain, physical function, stiffness, edema, quality of life and the secondary outcomes: adverse events, satisfaction with the treatment, rescue medication consumption and change in the structure of the linkage. From 2.241 studies found, 16 studies were included in systematic review and 9 were included in the meta-analysis. Only three studies fulfilled all validation criteria and presented a minimum risk of bias. *H. procumbens* had similar efficacy than diacerein, and presented better safety profile and less usage of rescue medication. *B. Serrata* was more effective than placebo and valdecoxib for the outcome pain and physical function, and presented low level of adverse events. The results of meta-analysis had not present benefit of use compared to *U. guianensis* in relation to placebo to reduce pain, but It was considered safe; no benefits were noticed from the *S. purpurea* and *S. daphnoides* in relation to placebo and to diclofenac for reduction pain, but had similar safety profile. *C. longa* was no superior to ibuprofen to pain reduction and physical function improvement, but it was considered the safest. *Z. officinalle* showed superiority compared to placebo in pain reduction, and presented similar safety profile to diclofenac and placebo. The results of this study should be carefully interpreted due to the low number of data included, which restrained the achievements. The results of this study should be viewed with caution due to low number of included studies. The evidence was not sufficient to support the safe and effective use of these herbal medicines to OA. Thus, this study guides managers of the Brazilian public health system and prescribers in the decision making regarding the use of these herbal medicines to OA.

Keywords: Osteoarthritis, Herbal medicine, Effectiveness, Safety.

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ACR	American College of Rheumatology
AINES	Anti-inflamatórios não esteróides
ANVISA	Agência Nacional de Vigilância Sanitária
CAPES	Brazilian database of Thesis of CAPES
CINHAL	Cumulative Index to Nursing and Allied Health Literature
COX	Ciclo-oxigenase
CENTRAL	Cochrane Central Register of Controlled Trials
EULAR	European League Against Rheumatism
GRADE	Grading of Recommendations Assessment, Development and Evaluation
MID	Minimally Important Difference
NF-Kb	Fator Nuclear kappa B
NSAID	non-steroidal anti-inflammatory drugs
OARSI	Sociedade Internacional para Pesquisa da Osteoartrite
OMS	Organização Mundial da Saúde
OA	Osteoartrite
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Clinical Trial
RENISUS	Relação Nacional de Plantas Medicinais de interesse ao Sistema Único de Saúde
SBR	Sociedade Brasileira de Reumatologia
SMD	Standardized mean difference
SUS	Brazilian Unified Health System
TNF-α	Fator de Necrose Tumoral alfa
VAS	Visual Analogue Scale
WMD	Weighted Mean Differences
WOMAC	Westerm Ontário and McMaster Universities
95%CI	95% confidence interval

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1 INTRODUÇÃO

O uso de medicamentos à base de plantas está amplamente difundido e encontra-se em expansão pelo mundo, variando significativamente entre os países, de acordo com práticas culturais, disponibilidade das plantas e programas de saúde nos países desenvolvidos e em desenvolvimento (BARNES et al., 2016). Devido serem largamente utilizados, a OMS (Organização Mundial de Saúde) relata que os desafios mais importantes são a determinação da segurança, eficácia e qualidade e a definição de regulamentação sanitária adequada destes fiteterápicos (WORLD HEALTH ORGANIZATION, 2005).

A partir de 1970 e 1980, em países desenvolvidos e em desenvolvimento, assim como o Brasil, ocorreu um crescimento importante das “medicinas alternativas”, entre elas a fitoterapia (LUZ, 1997). Em 1978 foi realizada a primeira Conferência Internacional sobre Cuidados Primários de Saúde, organizada pela OMS, que incentivou a valorização das terapias tradicionais e reconheceu oficialmente o uso de medicamentos à base de plantas com finalidade profilática, curativa e paliativa, quando recomendou a difusão mundial dos conhecimentos necessários para o seu uso (BRASIL, 2006a; ORGANIZAÇÃO PANAMERICANA DA SAÚDE, 1978). Desde então, em países industrializados e em desenvolvimento, as plantas medicinais representam a movimentação de milhões de dólares no mercado (GULLO; PEREIRA, 1998).

O Ministério da Saúde, por meio da Portaria nº 212, de 11 de setembro de 1981, que trata sobre as “Diretrizes e Prioridades de Investigação em Saúde” destacou o estudo de plantas medicinais como uma das prioridades de investigação em saúde (BRASIL, 1981). O uso de plantas medicinais foi regulamentado em 2006 pelo Decreto presidencial nº 5.813, em instância federal, que instituiu a Política Nacional de Plantas Medicinais e Fitoterápicos (BRASIL, 2006b). Também em 2006, de acordo com as recomendações da OMS foi publicada pelo Ministério da Saúde, a Política Nacional de Práticas Integrativas e Complementares no SUS (Sistema Único de Saúde), com a finalidade de ampliar as opções terapêuticas oferecidas aos usuários deste sistema, com garantia de acesso seguro e uso racional de plantas medicinais, fitoterápicos e outros serviços relacionados, com segurança, eficácia e

qualidade (BRASIL, 2006c). Estas políticas foram decisórias para a introdução do uso de plantas medicinais e de fitoterápicos no SUS (ANTONIO; TESSER; MORETTI, 2014).

A OMS considera medicamento fitoterápico aquele obtido com emprego de ervas, materiais ou preparações à base de plantas, produtos acabados a base de plantas que contenham partes de plantas e outros materiais vegetais ou suas combinações como ingredientes ativos (WORLD HEALTH ORGANIZATION, 2013).

Em países industrializados como Canadá, França, Alemanha e Itália, 70% a 90% da população têm usado esses recursos sobre a denominação de complementar, alternativo ou não convencional (WORLD HEALTH ORGANIZATION, 2011). Nos países em desenvolvimento, 80% das pessoas dependem da medicina tradicional e/ou complementar para suas necessidades básicas de saúde (SOLLER, 2000).

O crescimento na utilização de medicamentos fitoterápicos é atribuído às novas informações científicas sobre as propriedades medicinais das plantas, bem como, as preocupações dos consumidores sobre as reações adversas e contra-indicações para uso pessoal das modernas drogas sintéticas (SEWELL; RAFIEIAN-KOPAEI, 2014).

A utilização das plantas medicinais em pacientes acometidos por doenças reumáticas tem grande interesse científico (ERNST, 2000; JACOBS et al., 2001; SETTY & SIGAL, 2005; SOEKEN et al., 2003). Dentre as doenças reumáticas, a osteoartrite (OA) é a doença osteomuscular mais frequente e que leva ao declínio funcional e à perda significativa da qualidade de vida (PEREIRA; RAMOS; BRANCO, 2015), sendo uma das doenças músculo-esqueléticas mais debilitantes entre os idosos (MINNS et al., 2009).

O aumento da população de idosos no Brasil (INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA, 2002), remete a maior ocorrência nos casos de OA e consequente aumento de incapacidades, ocasionando um problema de saúde pública (DILLON et al., 2007).

Diversas diretrizes nacionais e internacionais para tratamento desta doença foram desenvolvidas ao longo dos anos. No Brasil, por meio do Projeto Diretrizes da AMB (Associação Médica Brasileira), a SBR (Sociedade Brasileira de

Reumatologia), publicou em 2003 um consenso para o tratamento da OA (COIMBRA et al., 2004). Em 2010, a OARSI (Sociedade Internacional para Pesquisa da Osteoartrite) publicou seu guia de recomendações baseado em publicações de maior qualidade de evidência e rigor metodológico (ZHANG et al., 2010).

O uso de medicamentos é complementar às medidas não farmacológicas, sendo os medicamentos de primeira escolha, os analgésicos e os AINES (anti-inflamatórios não esteroides), controversos por seus eventos adversos gastrointestinais e cardiovasculares e elevado custo (RANNOU; PELLETIER; PELLETIER, 2016; REZENDE; GOBBI, 2009). Diante deste quadro, alternativas são de grande interesse.

Duas revisões sistemáticas avaliaram o uso de medicamentos a base de plantas para o tratamento da OA para uso tópico (CAMERON; CHRUBASIK, 2013) e oral (CAMERON; CHRUBASIK, 2014). No entanto, estes estudos não incluíram algumas plantas comercializadas no Brasil.

No Brasil, 13 plantas sob a forma de medicamentos fitoterápicos são comercializadas para o tratamento da OA: *Harpagophytum procumbens* DC. ex Meisn., *Uncaria tomentosa (Willd.)* DC., *Salix alba* L., *Curcuma longa* L. (ou *Curcuma domestica* Valeton), *Chenopodium ambrosioides* L., *Cordia curassavica (*Jacq.) Roem. & Schult. (ou *Cordia verbenacea* DC.), *Zingiber officinale* Roscoe, *Persea* gratissima Gaertn.f. (ou *Persea americana* Mill.), *Boswellia serrata* Roxb. ex Colebr., *Bowdichia virgilioides* Kunth., *Salix daphnoides Vill*., *Salix purpurea* L. e *Uncaria guianensis* (Aubl.) J.F. Gmel (Quadro 01).

Apesar da diversidade de fitoterápicos disponíveis no Brasil para tratar a OA, a segurança e a efetividade da maioria destes agentes é incerta. Este estudo desenvolveu uma revisão sistemática e metanálise dos medicamentos à base de plantas medicinais para uso oral, comercializados no Brasil para o tratamento da OA.

Quadro 1. Fitoterápicos com indicação para osteoartrite comercializados no Brasil

Fitoterápicos comercializados no Brasil/nome popular	**Financiados pelo governo**	**Plantas que estão na RENISUS**
H. procumbens. (Garra do diabo)	**X**	
U. tomentosa (Unha de gato)	**X**	
S. alba (Salgueiro branco)	**X**	
C. longa ou C. domestica (Açafrão da terra)		**X**
C. ambrosioides (Erva de Santa Maria)		**X**
C. curassavica ou C. verbenacea (Erva baleeira)		**X**
Z. officinale (Gengibre)		**X**
P. gratissima ou P. americana (Abacateiro)		**X**
S. purpurea (Salgueiro de casca roxa)	**-**	-
U. guianensis (Unha de gato)	**-**	-
B. serrata (Salai guggal)	**-**	-
B. virgilioides (Sucupira preta)	**-**	-
S. daphnoides (Salgueiro violeta)	**-**	-

Fonte: Elaboração própria. RENISUS (Relação Nacional de Plantas de Interesse ao SUS).
– (não pertencem a nenhuma das listas).

2 REFERENCIAL TEÓRICO

2.1 Osteoartrite (OA)

A OA afeta as articulações sinoviais causando degradação e perda de cartilagem articular, crescimento anormal do osso subcondral, remodelação óssea, e nas fases iniciais, a inflamação da sinóvia (HUNTER, 2011; LITWIC et al., 2013). Qualquer articulação do corpo pode ser afetada, sendo as mais prevalentes as do quadril, joelhos, mãos e coluna (WOLFSDAT et al., 2015).

A complexidade da OA tem dificultado as tentativas de entender sua etiologia, a qual ainda permanece indefinida. No entanto, um conjunto de fatores de risco conhecidos está associado à doença incluindo: idade, sexo, obesidade, sedentarismo e trauma articular prévio (JOHNSON; HUNTER, 2014; LOESER, 2013). Afeta mais as mulheres que os homens e sua prevalência aumenta com o aumento da idade, sendo causa principal de dor, deficiência crônica em adultos (LEONG et al., 2013) e incapacidade em idosos (LAWRENCE et al., 2008).

O risco de desenvolver OA do joelho sintomática é estimado em aproximadamente 17% e 10% para OA sintomática de quadril com base em dados do projeto OA de *Johnston County* (JOHNSON; HUNTER, 2014). Os riscos aumentam para 60,5% entre as pessoas obesas (MURPHY et al., 2008) e o trabalho físico pesado pode explicar a OA em alguns casos (VAN DEN BERG, 2010; ZHANG; JORDAN, 2010).

A doença desenvolve progressivamente ao longo de vários anos, em resposta à falha progressiva de condrócitos para reparar cartilagem articular danificada nas articulações sinoviais (BARRY; MURPHY, 2013; BIJISMA; BERENBAUM; LAFEBER, 2011). As articulaçoes submetidas a esta doença não resistem às solicitações mecânicas normais, devido ao aumento da síntese de proteinases destrutivas de tecido e a apoptose de condrócitos, bem como, a geração de quantidades insuficientes de matriz extracelular (BIJISMA; BERENBAUM; LAFEBER, 2011).

As manifestações clínicas da OA incluem dor nas articulações, rigidez, ternura, inchaço e perda de movimento; bem como insônia, síndrome das pernas inquietas e hipersonia (PICKERING et al., 2015). Além disso, à medida que a

cartilagem diminui, a superfície óssea pode ser afetada, o que resulta no desenvolvimento de osteófitos e contato direto osso-osso que leva a movimentos restritos causando atrofia muscular e flacidez dos ligamentos (GUPTA et al., 2012).

Embora não existam terapias curativas para esta doença, alguns tratamentos disponíveis podem ajudar a aliviar os sintomas (BORNES; ADESIDA; JOMBA, 2014; LE GRAVERAND, 2010). As medidas terapêuticas iniciais incluem tratamentos não farmacológicos como educação do paciente, perda de peso e fisioterapia (AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS, 2013).

Os tratamentos farmacológicos aliviam os sintomas persistentes (KOGA et al., 2009; LI et al., 2014), sendo usados analgésicos e AINES na doença sintomática. No entanto, estes últimos, podem apresentar eventos adversos importantes gastrointestinais e cardiovasculares (SOSTRES et al., 2010). O tratamento cirúrgico é reservado como último recurso para controlar os sintomas em pacientes com doença refratária (KAHAN et al., 2009; LI et al., 2014; PAVELKA et al., 2002).

2.2 Plantas medicinais comercializadas no Brasil para tratamento da osteoartrite

2.2.1 Boswellia serrata Roxb. ex Colebr.

Popularmente chamada de “Salai guggal”, pertencente a familia Burseraceae, é uma grande árvore com ramificação que cresce em regiões montanhosas secas da Índia, da África do Norte e Oriente Médio (LEUNG; FOSTER, 1996; WALLIS, 1967). O extrato é obtido da incisão feita no tronco da árvore e possui forte indicação para doenças inflamatórias crônicas (HARTMANN et al., 2012; SIDDIQUI, 2011).

Publicações apontam fortemente para a sua utilização devido ao efeito anti-inflamatório, anti-hiperlipidémico, anti-aterosclerótico, analgésico e hepatoprotetor (DHIMAN, 2006; MATHE; CULIOLI; ARCHIER, 2004; SHARMA; THAWANI; HINGORANI, 2004). Estudos em modelos animais mostram que os ácidos boswélicos inibem a síntese da enzima pró-inflamatória (AMMON et al., 1991; ETZEL, 1996). A forma mais encontrada é o extrato de resina de goma que tipicamente contém 30% de ácidos boswélicos (SHARMA; THAWANI; HINGORANI, 2004), sendo que algumas fontes comerciais podem conter até 65%. A dose ideal

varia de acordo com o fabricante, o que torna difícil a padronização (SIDDIQUI, 2011).

2.2.2 Bowdichia virgilioides Kunth.

Árvores do gênero Pterodon, popularmente conhecida como "Sucupira preta", são nativas da região central do Brasil. Os frutos são vagens pequenas, achatadas, indeiscentes, com mais de uma semente cada, fato que a distingue da espécie *Pterodon emarginatus*, cujo fruto contém apenas uma semente, com propriedades medicinais. É considerada uma planta pioneira e adaptada a terrenos secos e pobres (BRANDÃO; FERREIRA, 1991; LORENZI, 1992).

Os frutos são vendidos em mercados populares e são utilizados na medicina tradicional, ingeridos em pequenas quantidades e em intervalos de tempo regulares para o tratamento de reumatismo, dor de garganta e doenças respiratórias (bronquite e amigdalite). Também possuem propriedades anti-inflamatória, analgésica e hipoglicêmica (ARRIAGA et al., 2000; LEONHARDT et al., 2010).

Estudos fitoquímicos no gênero Pterodon têm demonstrado a presença de isoflavonas, sesquiterpenos e diterpenos no óleo de seus frutos (ARRIAGA et al., 2000; DUTRA et al., 2012; PINTO et al., 2013); isoflavonas e triterpenos na madeira (MARQUES et al., 1998); alcaloides, saponinas, glicosídeos, esteroides na casca das árvores (BUSTAMANTE et al., 2010); esteroides, sesquiterpenos, isoflavonas, saponinas nas folhas (NEGRI; MATTEI; MENDES, 2014). Os extratos dessa espécie possui propriedades anti-inflamatórias em condições inflamatórias agudas (BARROS et al., 2010).

Carvalho et al. (1999) sugeriram que a atividade anti-inflamatória do extrato pode estar relacionada com a presença de compostos de terpenos. Estudos *in vitro* e *in vivo* confirmaram essas atividades e procuraram desenvolver fitoterápicos, utilizando métodos que preservam o conteúdo do material vegetal. Além disso, as avaliações de toxicidade indicam que a terapêutica feita a partir de espécies Pterodon é segura quando tomadas nas doses recomendadas (COELHO; SABINO; DALMAU, 2004; LEAL et al., 2000; SABINO et al., 1999).

2.2.3 Chenopodium ambrosioides L.

Trata-se de uma planta da família Amaranthaceae, nativa da América, originária do México, porém, pode ser encontrada em todos os países de clima temperado e tropical. No Brasil, encontra-se distribuída em quase todo o território nacional onde é conhecida popularmente como “Erva de Santa Maria” (LIMA; MAGALHÃES; SANTOS, 2011). Sua composição química, em média, 60% de (Z)-ascaridol,18% de (E)-ascaridol e 3% de carvacrol como principais constituintes do óleo essencial desta planta (JARDIM, 2006).

Algumas ações biológicas desta planta têm sido cientificamente demonstradas, especialmente em estudos utilizando os extratos de suas folhas: modulação das respostas imunes e inflamatórias (PINHEIRO et al., 2005); antitumor (NASCIMENTO et al., 2006), analgésico e anti-inflamatório (SOUSA et al., 2012; TRIVELLATO et al., 2013). Ibironke e Ajiboye (2007) estudaram a atividade anti-inflamatória e antinociceptiva do extrato de folhas secas de *C. ambrosioides* em camundongos e encontraram diminuição do processo inflamatório.

Em 2009, o Ministério da Saúde selecionou a *C. ambrosioides* para RENISUS considerando seu uso na medicina popular e seu potencial na terapêutica da inflamação, dor e cicatrização. Embora popularmente muito utilizada, pouco se sabe a respeito dos benefícios e riscos do seu uso no tratamento da OA (RELAÇÃO NACIONAL DE PLANTAS MEDICINAIS DE INTERESSE AO SUS, 2009).

2.2.4 Cordia curassavica (Jacq.) Roem. & Schult. (ou *Cordia verbenacea* DC.)

Pertencente à família Boraginaceae, é popularmente conhecida por “Erva-baleeira” (AKISUE et al., 1983) e tem como sinonímia científica principal, *C. verbenacea* DC. (LORENZI, 2002). A espécie é nativa da América tropical, mas também, tem sido amplamente introduzida para o Sudeste Asiático e na região do Pacífico tropical, onde é uma erva invasora (FICARRA; TOMMASNI, 1995). Ocorre no Brasil do Amazonas até o Rio Grande do Sul, nas proximidades do mar (ANGELY, 1970).

Alguns estudos têm demonstrado as características químicas e o potencial medicinal da *C. curassavica*. Kaufmann (2002) isolou do extrato etanólico o β-sitosterol e duas flavonas, sendo uma delas a artemetina. Velde et al. (1982) estudando o extrato acetônico das folhas, isolaram dois novos triterpenos,

denominados cordialina A e cordialina B. Loset et al. (2000) identificaram quatro naftoquinonas (cordiaquinonas A, B, J e K) nos extratos diclorometânicos das raízes de *C. curassavica.*

O extrato etanóico é muito utilizado pela população, principalmente litorânea, no tratamento de diversos processos inflamatórios. Alguns autores observaram tal atividade biológica (AKISUE et al., 1983; SERTIÉ et al., 1991) e sugeriram que o flavonóide artemetina seja o princípio ativo responsável pela atividade anti-inflamatória dessa espécie (BASILE et al., 1989; SERTIÉ et al., 1991).

A Erva baleeira é uma das 71 espécies vegetais com potencial de avançar nas etapas da cadeia produtiva e de gerar produtos de interesse ao SUS e ao Ministério da Sáude (RELAÇÃO NACIONAL DE PLANTAS MEDICINAIS DE INTERESSE AO SUS, 2009).

2.2.5 Curcuma longa L. (ou *Curcuma domestica* Valeton)

Conhecida no mercado internacional como "*turmeric*" e popularmente chamada no Brasil como “Açafrão da terra”, a *C. longa*, membro da família Zingiberaceae, é nativa da Índia e sudeste da Ásia, onde a raiz fresca é amplamente utilizada de maneira semelhante ao gengibre. No Ocidente, açafrão é muito mais comumente disponível como um pó seco (PRABHAKAR et al., 2013).

Utilizada tradicionalmente, o rizoma é a principal parte da planta empregada nas preparações com benefícios principalmente para artrite (MOLLIK et al., 2009; SHARMA et al., 2009) e OA (BADRIA et al., 2002; KERTIA et al., 2012; KULKARNI et al., 1991; KUPTNIRATSAIKUL et al., 2009; MADHU; CHANDA; SAJI, 2013).

Sabe-se que a curcumina é o principal componente do açafrão, responsável pelas suas atividades biológicas (PRABHAKAR et al., 2013) e está presente nos rizomas em concentração que varia de 2,8 a 8% (GOVINDARAJAN, 1980). Denomina-se curcumina ao conjunto dos três compostos: curcumina, demetoxicurcumina e bisdemetoxi-curcumina (TAKAHASHI, 1987). Esses três compostos aparecem em proporções variáveis nos rizomas e, por apresentarem espectro de absorção numa pequena amplitude de 420 a 425nm, tornou-se prática usual expressar simplesmente por curcumina (RUSIG; MARTINS, 1992).

A curcumina atua em vários níveis da cascata de inflamação: ela modula a produção de interleucinas pró-inflamatórias e diminui a ação da fosfolipase A2, ciclooxigenase-2 e 5-lipoxigenase. Curcumina não afeta a atividade de COX-1, o que contribui para a sua excelente tolerância. A sua ação anti-inflamatória é devida à modulação do fator nuclear kappa-B (NFkB), responsável pela atividade anti-catabólica e outros fatores de transcrição (PRASAD et al., 2014).

Estudos epidemiológicos sugerem que a curcumina possui propriedades anti-inflamatórias, hipolipemiantes, antitrombóticas, antitumoral, anti-diabéticas e neuroprotetoras (SHEHZAD; REHMAN; LEE, 2013). Estudos *in vitro* revelaram efeito protetor sobre a cartilagem (HENROTIN; PRIEM; MOBASHERI, 2013). A *C. longa* encontra-se incluída na RENISUS (RELAÇÃO NACIONAL DE PLANTAS MEDICINAIS DE INTERESSE AO SUS, 2009).

2.2.6 Harpagophytum procumbens DC. ex Meisn

Pertencente à familia Pedaliaceae, é comumente chamado de “Garra do diabo”. É uma planta herbácea nativa do sul da África (VAN WHY; GERICKE, 2000). Não são encontrados relatos de ocorrência da espécie no Brasil (GRANT et al., 2007).

O harpagosídeo é apontado como o constituinte ativo majoritário da espécie (MNCWANGI et al., 2012), responsável pela atividade anti-inflamatória. Outros constituintes químicos descritos para as raízes de *H. procumbens* são iridoides, flavonoides, harpagoquinones, aminoácidos, fitoesteroides e hidratos de carbono (CAPRASSE, 1980; GRUENWALD, 2002).

Estudos mostram que as raízes tuberosas da planta são tradicionalmente utilizadas como anti-inflamatórios no tratamento da dor, sendo eficazes na artrite reumatoide, OA, tendinite, inflamação do rim, doença do coração, dispepsia e perda do apetite (STEWART; COLE, 2005; WICHTIL; BISSET, 2000).

Extratos em pó, aquosos e alcoólicos a partir das raízes da planta, são usados como medicamentos de forma tradicional para OA e dor lombar (CHRUBASIK; CONRADT; BLACK, 2003).

Postula-se que a eficácia de *H. procumbens* pode ser explicada pela sua capacidade de bloqueio da produção de mediadores inflamatórios, tais como a

prostaglandina E2 (ABERHAM et al., 2007). Das 71 espécies de plantas incluídas na RENISUS, o *H. procumbens* encontra-se entre as 8 aprovadas pela ANVISA (Agência Nacional de Vigilância Sanitária) para ser distribuída para a população pela rede pública de saúde.

2.2.7 *Persea gratissima* Gaertn. f.J.F. Gmel.

Também conhecida como *Persea americana* e popularente chamada de "Abacateiro", é uma árvore pertencente à família Lauraceae, nativa da América Central e, atualmente encontrada em regiões tropicais e subtropicais. O uso medicinal da planta de abacate consiste nas folhas secas (ROSAS-PINÓN et al. 2012) que contenham pelo menos 0,4% de flavonoides totais expressos em apigenina e 0,14% de óleo essencial (BRASIL, 2009).

Adeyemi, Okpo e Ogunti (2002) avaliaram o potencial anti-inflamatório e analgésico do extrato aquoso de folhas de abacate em camundongos e encontraram inibição da dor e da inflamação de forma dependente da dose. Outras pesquisas têm evidenciado que seu extrato aquoso tem atividade analgésica e anti-inflamatória comparável ao ácido acetilsalicílico (YASIR; DAS; KHARYA, 2010). Esta planta também consta na RENISUS (RELAÇÃO NACIONAL DE PLANTAS MEDICINAIS DE INTERESSE AO SUS, 2009).

2.2.8 Salix alba L., *Salix daphnoides* Vill. *e Salix purpurea* L.

Também conhecidas de forma geral como "*Willow bark"* ou "Casca de salgueiro", são componentes de muitos fármacos à base de plantas devido às propriedades analgésicas e antipiréticas (WALSH, 2002). O *Willow bark* possui teor de salicina, composto produzido da casca do salgueiro com propriedades analgésicas e anti-inflamatórias. No entanto, ensaios clínicos sugerem que outros compostos presentes como polifenóis, flavonóides e fenóis simples podem contribuir para os efeitos terapêuticos (SCHIMID; KOTTER; HEIDE, 2001; KHAYYAL et al., 2005).

Atualmente há grande interesse no uso de medicamentos feitos da casca de salgueiro para tratamento de dor crônica, visto que o uso de analgésicos e anti-inflamatórios pode ser menos seguro (NAKAMURA et al., 2009; LI et al., 2014).

O gênero Salix inclui as espécies: *S.alba* (Salgueiro branco), *S. daphnoides* (Salgueiro violeta) e *S. purpurea* (Salgueiro de casca roxa) entre outras que são vendidas sob o rótulo de casca de salgueiro. A espécie *S. alba* é a mais usada com propósitos medicinais e aprovada pela Anvisa para ser distribuída pela rede pública (RELAÇÃO NACIONAL DE PLANTAS MEDICINAIS DE INTERESSE AO SUS, 2009).

2.2.9 *Uncaria tomentosa* (Willd.) DC. e *Uncaria guianensis* (Aubl.) J.F. Gmel.

Existe uma grande variedade de espécies conhecidas como “unha-de-gato”, porém, as duas mais famosas por suas propriedades antioxidantes e anti-inflamatórias pertencem ao gênero Uncaria, são *U. tomentosa e U. guianensis* (OBREGON, 1995). A característica principal dessas espécies são os espinhos em forma de garra de gato.

A *U. tomentosa* é uma planta trepadeira que possui espinhos semicurvados e a *U. guianensis* é rasteira, de menor tamanho e apresenta dificuldade de subir porque possui espinhos curvados, em forma de chifre de carneiro. Ambas ocorrem nas zonas tropicais do Brasil, Peru, Venezuela, Colômbia, Bolívia, Guianas e Paraguai (ALEXIADES, 2002).

A casca e a raiz são as partes da planta mais frequentemente usadas (WILLIAMS, 2001). Estas plantas são usadas indistintamente na medicina tradicional, contudo, há falta de dados científicos comparando a eficácia das espécies. A padronização de formulações comerciais de unha de gato é baseada no teor de alcaloides. Preparações de *U. tomentosa* têm sido preferidas devido ao maior teor de alcaloides e facilidade de padronização (SANDOVAL et al., 2002).

Vários grupos relataram a presença de uma grande variedade de constituintes químicos na unha de gato, como: alcaloides oxíndole (praticamente ausentes em *U. guianensis*), polifenóis (flavonoides, proantocianidinas), quinovico α-glicosídeos, alcaloides pentacíclicos e esterois (AQUINO et al., 1991; LAUS; BROSSENER; KEPLINGER, 1997; SENATORE et al., 1989). No entanto, alguns estudos demonstraram que estes componentes isolados exercem consistente efeito anti-inflamatório (AQUINO et al., 1990).

Há relatos de sua efetividade no tratamento de doenças inflamatórias como artrite e asma (CISNEROS; JAYO; NIEDZIELA, 2005; SETTY; SIGAL, 2005). A capacidade de unha de gato em reduzir a produção de TNF- α (Fator de Necrose Tumoral alfa) em baixas concentrações sugere que a mesma pode ser uma terapia adjuvante excelente na inflamação crônica, em transtornos caracterizados por uma resposta excessiva, em particular da produção de TNF-α (SANDOVAL-CHACO'N et al., 1998). Foi verificado ainda que a planta possa proteger as células contra o estresse oxidativo por impedir a ativação do NF-Kb (Fator Nuclear kappa B) (CISNEROS; JAYO; NIEDZIELA, 2005).

Estudos suportam o uso sozinho ou em combinação com outras ervas medicinais para o tratamento da OA (MEHTA et al., 2007). *U. tomentosa* é um dos fitoterápicos recomendados para ser distribuído pelo SUS.

2.2.10 *Zingiber officinale* Roscoe.

Conhecido como "gengibre", é uma planta herbácea e perene da família das Zingiberaceae, originária da Índia e Ásia, de onde se difundiu pelas regiões tropicais do mundo. No Brasil, o gengibre é cultivado principalmente na faixa litorânea do Espírito Santo, Santa Catarina, Paraná e no sul de São Paulo, em razão das condições de clima e de solo mais adequadas (SILVA; CARVALHO, 2004; ZHOU; DENG; XIE, 2006). O seu caule duro, grosso e subterrâneo é utilizado mundialmente como especiaria e na preparação de medicamentos (PARTHASARATHY; CHEMPAKAM; ZACHARIAH, 2008).

As propriedades únicas de sabor do gengibre surgem da combinação de óleo essencial aromático. Os principais compostos pungentes em gengibre fresco são uma série de cetonas fenólicas homólogas conhecidas como gingerols. O rizoma de gengibre também contém resina, proteínas, celulose, pentosanas, amido e elementos minerais. Destes, o amido é o mais abundante e compreende 40-60% do rizoma numa base de peso seco. A abundância relativa de determinados constituintes do gengibre é determinada pela forma de cultivo, condições ambientais e estágio de maturação na colheita (PARTHASARATHY; CHEMPAKAM; ZACHARIAH, 2008).

Os gigerols foram relacionados a vários efeitos farmacológicos e fisiológicos, incluindo antioxidante (MASUDA et al., 2004), anti-inflamatório, analgésico (YOUNG et al., 2005), antipirético, gastroprotetor (SUEKAWA et al., 1984), cardiotônicos (KOBAYASHI; SHOJI; OHIZUMI, 1987), dentre outros.

A planta tem sido usada a milhares de anos na medicina Ayurveda para o tratamento da inflamação e reumatismo. Estudos sugerem que o óleo de gengibre pode ser usado para artrite e dores crônicas associadas à inflamação (ZHOU; DENG; XIE, 2006), sendo que sua ação justifica-se pela inibição da ciclooxigenase (COX), da biossíntese de leucotrienos e de TNF-alfa (SETTY; SIGAL, 2005).

3 OBJETIVOS

3.1 Primário

Avaliar a efetividade e segurança dos medicamentos de uso oral à base de plantas medicinais comercializados no Brasil para o tratamento da OA, por meio de revisão sistemática e metanálise.

3.2 Secundários

- Determinar a efetividade e segurança dos fitoterápicos usados no tratamento da OA em comparação com placebo ou outros tratamentos.
- Determinar as diferenças entre estes medicamentos em relação à efetividade e segurança.
- Definir a qualidade da evidência dos dados produzidos nesta revisão.

4 RESULTADOS

Esta dissertação é apresentada no formato de artigo científico, elaborado conforme as recomendações do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba (Anexo A).

O artigo referente ao protocolo do estudo foi publicado no periódico “Systematic Reviews” (Anexo B) e está disponível no apêndice A. O artigo 2 está descrito a seguir.

Title: Herbal medicine oral marketed in Brazil for treatment of osteoarthritis: A Systematic Review and Meta-analysis

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Abstract

Background: Osteoarthritis (OA) affects 1% of the world's population and is the most common cause of musculoskeletal impairment in the elderly. Herbal medications are commonly used in Brazil to manage symptoms associated with OA and some of them are financed by Brazilian government; however, the effectiveness of most of these agents is uncertain. This study systematically reviewed the effectiveness and safety of 13 oral herbal medications used in Brazil for the treatment of OA. **Methods:** Randomized clinical trials (RCT) eligible enrolled adults with OA treated by a herbal medicine or a control group (placebo or active control) were searched in the following electronic databases: CENTRAL; MEDLINE; EMBASE; CINAHL; Web of Science; Health Star; AMED, the database of the Cochrane Complementary Medicine Field, LILACS; CAB abstracts, Clinical trial.gov, WHO trials registry, and Brazilian database of Thesis (CAPES) and trial register in Brazil (REBEC), to May 2016, without restrictions concerning to language or status of publication. Primary outcomes were: pain in overall, physical function, swelling, stiffness and quality of life ant the secondary outcomes were: adverse events, activity limitations, satisfaction with the treatment. Dichotomous data were summarized as risk ratios; continuous data were given as standard average differences with 95% confidence intervals. A team of reviewers evaluated each citation independently for eligibility and in duplicate it. For eligible studies, the same reviewers conducted data extraction and bias risk assessment, and will determinate of the overall quality of evidence for each of the outcomes using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) classification system.

Results: From 2,241 studies found, 16 studies with 1,741 patients were included in SR, and 9 were included in the meta-analysis (corresponding to seven of the 13 herbal medicines studied: *B. serrata* (n=2), *C. longa* ou *C. domestica* (n=3), *H. procumbens* (n=1), *S. daphnoides, S. purpurea* (n=3*), U. guianensis* (n=2), *Z. officinale* (n=5). Only three studies (18.75%) fulfilled all validation criteria and presented a minimum risk of bias. *H. procumbens* had similar efficacy than diacerein, and presented better safety profile. *B. Serrata* was more effective than placebo and valdecoxib for the outcome pain and physical function, and presented be safe. The results of meta-analysis showed no benefit of *U. guianensis* in relation to placebo to

reduce pain, and didn't present adverse events.*S. purpurea* and *S. daphnoides* were similar in relation to placebo and diclofenac for reduction pain and had similar safety profile. *C. longa* was no superior to ibuprofen to pain reduction and physical function improvement, but it was considered the safest. *Z. officinalle* showed superiority compared to placebo in pain reduction, and presented similar safety profile to diclofenac and placebo.

Conclusions: The results of this study should be carefully interpreted due to the low number of data included, which restrained the achievements. The evidence was not sufficient to support the safe and effective use of these herbal medicines to OA. Thus, this study guides managers of the Brazilian public health system and prescribers in the decision making regarding the use of these herbal medicines to OA

Keywords: Osteoarthritis, Herbal medicine, Effectiveness, Safety.

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disease and is associated with significant functional decline and reduced quality of life (PEREIRA; RAMOS; BRANCO, 2015). It is characterized by loss of articular cartilage, subchondral bone remodeling, bone spurs, ligament laxity, weakening of the periarticular muscles, and thickening of the capsule and synovial membrane (LITWIC et al., 2013). It is the result of both mechanical and biological events that cause imbalance in the normal process of degradation and synthesis of joint cartilage chondrocyte, extracellular matrix, and subchondral bone (HUNTER; FELSON, 2006) and can be associated with pain, stiffness and functional limitations (BUSIJA et al., 2010).

OA affects more women than men, being the main cause of pain, chronic deficiency in adults (LEONG et al., 2013) and disability in the elderly (ZHANG; WANG, 2015). The World Health Organization (WHO) states that OA is a disease related to an aging population (WOOLF; PLEGER, 2003). The risk increases from 1% in 30-years old people to almost 10% in people over the age of 40 years and 50% in people over the age of 60 years (KELLEY'S TEXTBOOK OF RHEUMATOLOGY, 2001). Disease produces a variety of serious social problems, both healths as economic (MINNS et al., 2009).

The drugs are considered complementary to non-pharmacological measures and non-steroidal anti-inflammatory drugs (NSAID) are the drugs of choice, despite of gastrointestinal adverse events and cardiovascular and high cost (RANNOU; PELLETIER; PELLETIER, 2016). Therefore, alternatives are of great interest.

The use of herbal medicines worldwide is substantial and increasing varying significantly between countries, according to cultural practices, availability of plants and health programs in developed and developing countries (BARNES et al., 2016). In developed countries such as Canada, France, Germany and Italy, 70% to 90% of the population have used these features on the supplementary denomination, alternative or unconventional (WORLD HEALTH ORGANIZATION, 2011). How are widely used, the World Health Organization (WHO) reports that the most important challenges are the safety, efficacy and quality, and the definition of adequate health regulations (WORLD HEALTH ORGANIZATION, 2005).

The Brazilian Policy of Integrative and Complementary Practices and the National Policy of Medicinal and Phytotherapeutic Plants adopted in 2006 were created to meet the demands of the Brazilian population. These policies were decisive steps towards introducing the use of medicinal and phytotherapeutic plants in the Brazilian Unified Health System (SUS) (ANTONIO; TESSER; MORETTI-PIRES, 2014).

The growth in the use of herbal medicines is attributed to new scientific information on the medicinal properties of plants, as well as consumer concerns about adverse reactions and contraindications for personal use of modern synthetic drugs (SEWELL; RAFIEIAN-KOPAEI, 2014).

Two systematic reviews have evaluated the use of herbal medicinal products for the treatment of OA for oral (CAMERON; CHRUBASIK, 2014) and topical use (CAMERON; CHRUBASIK, 2013). However, these studies did not include some plants which are sold in Brazil.

In Brazil, there are 13 herbal medications marketed for treatment of OA: *Harpagophytum procumbens* DC. ex Meisn. (Devil's claw), *Uncaria tomentosa* (Willd.) DC. (C*at's claw*), *Salix alba* L. (White willow)*,* (financed by government), *Curcuma longa* L. (or *Curcuma domestica* Valeton) (Turmeric), *Chenopodium ambrosioides* L. (Santa Maria herb*)*, *Cordia curassavica* (Jacq.) Roem. & Schult. (or

Cordia verbenacea DC.) (Whaler herb), *Zingiber officinale* Roscoe (Ginger), *Persea gratissima* Gaertn.f. (or *Persea americana* Mill.) (Avocado), (they are in the National List of Medicinal Plants of Interest to the Unified Health System - RENISUS), *Boswellia serrata* Roxb. ex Colebr. (Salai guggal), *Bowdichia virgilioides* Kunth. (Black sucupira), *Salix daphnoides* Vill (violet willow), *Salix purpurea* L. (Purple shell willow) and *Uncaria guianensis* (Aubl.) J.F. Gmel (Cat's claw).

Despite the common use of herbal medications to manage OA, the safety and effectiveness of some of these agents are uncertain. We therefore conducted a systematic review and meta-analysis of oral herbal medications used in Brazil for the treatment of OA.

Methods

Standards and Protocol Register

The systematic review was performed according to the recommendations specified in the Cochrane Handbook for Interventional Reviews and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (SHAMSEER et al., 2015). This protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO-CRD42015019793 - http://www.crd.york.ac.uk/PROSPERO/).

Eligibility criteria

Inclusion criteria

Patients: Adults (>18 years old) with a diagnosis of OA according to the criteria of American College of Rheumatology (ACR): Western Ontario and McMaster Universities (WOMAC) (ALTMAN et al., 1991) or the equivalent criterion of European League Against Rheumatism (EULAR): Lequesne index (ZHANG; JORDAN, 2010).

Interventions: One of the 13 oral herbal medicines used by Brazilian population from any of the following plant preparations (whole, powder, extract, crude drug, standardized mixture and drug extract ratio and solvent): *B. serrata*, *B. virgilioides*, C. *longa* (or *C. domestica*), *C. ambrosioides*, *C. curassavica* (or *C. verbenacea*), *H. procumbens*, *P. gratissima* (or *P. americana*), *S. alba*, *S. daphnoides*, *S. purpurea*, *U. tomentosa*, *U. guianensis* and *Z. officinale*, compared to

a control group in which patients receive placebo or a non-herbal medicine controls (for example, NSAID). We identified the daily dose, the active principles and the marker substance of each plant.

Study type: Randomized Controlled Trials (RCT).

Exclusion criteria

Patients: Studies in which more than 20% of patients have other associated disease.

Interventions: Studies that investigated the simultaneous use of more than one of the eligible plants were excluded.

Measure outcomes

Our outcomes were consistent with those proposed by the Cochrane Musculoskeletal Group systematic intervention reviews for OA (PHAM et al., 2004) and when necessary, the results were evaluated to unification of the different scales.

The primary outcomes were: pain (in overall, at rest, movement or night) (Visual Analogue Scale - VAS, pain scale sub Westerm Ontario and McMaster Universities - WOMAC index; Lequesne index and other scales); physical function - global disability or walking disability (VAS, sub function scale sub WOMAC index; Lequesne index and other scales); swelling (VAS and other scales); stiffness (VAS, stiffness scale sub WOMAC index; Lequesne index and other scales); quality of life (Short Form-36 and other scales).

The secondary outcomes were: adverse events (withdrawals and serious adverse events - that cause death, life-threatening, hospitalization, disability or permanent damage); number of patients reporting any adverse effects, activity limitations; satisfaction with the treatment; consume of rescue medication; duration of symptom resolved; change in the structure of the joint (according to American College of Rheumatology criteria for OA classification).

Search methods for primary studies

Electronic searches

We searched the following electronic databases: the CENTRAL (Cochrane Central Register of Controlled Trials), MEDLINE, EMBASE, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Web of Science, Health Star (via OVID), AMED, LILACS, CAB abstracts, clinical trial.gov, the WHO Trial Register and the Brazilian thesis database (CAPES) to 31st May 2016; without language and status of publication restrictions. We combined the terms that describe OA and herbal medications, individually (appendix B).

Searching other resources

We reviewed the reference list of every eligible study and review articles to identify additional eligible trials. We wrote to the authors of all eligible trials and the pharmaceutical companies involved in the production of herbal medicines and inquire about additional trials of which they are aware. Five Brazilian scientific journals were also searched by hand for additional eligible studies (Journal of Basic and Applied Pharmaceutical Sciences, Brazilian Journal of Pharmacy, Brazilian Journal of Pharmacognosy, Brazilian Journal of Medicinal Plants and Brazilian Journal of Pharmaceutical Sciences). Unpublished studies were identified by searching in reference lists reported in the Brazilian legislation and conference proceedings (Medicinal Symposium of Brazilian medicinal plants; International Congress of Ethnopharmacology).

Search strategy

The search was conducted individually for each plant. The following MeSH terms were used: 1) intervention (scientific name of plant, synonymies of each medicinal plant; popular name of each medicinal plant); 2) condition (osteoarthritis, ostepathritis, osteoarthritides, osteoarthrosis, osteoarthroses, arthritis, degenerative, arthritides, degenerative, degenerative arthritides, degenerative arthritis and osteoarthrosis deformans). We adapted the search strategy for each database (appendix C).

Eligibility determination

Four reviewers (CC, MG, MB and SK), working in pairs, independently screened potentially relevant citations and abstracts and applied the selection criteria. The full texts of all articles that either reviewer feels might be eligible were obtained. Two reviewers independently rated the eligibility of each full-text article and resolved disagreements by consensus. In case of duplicate publication, were used the article with the more complete data.

Data extraction

Four reviewers (CC, MG, MB and SK), working in pairs, independently extracted the data and recorded information regarding patients, methods, interventions, outcomes, and missing outcome data using standardized and pretested data extraction forms with instructions. Before starting data extraction, was conducted calibration exercises to ensure consistency between reviewers. We contacted study authors to resolve any uncertainties. Disagreements were resolved by consensus with any unresolved issues referred to another reviewer.

Risk of bias in individual studies

Using a modified version of the Cochrane collaboration risk of bias tool (ALTMAN et al. 1990; HIGGINS; GREEN, 2011) the same pairs of reviewers independently rated the risk of bias for each randomized trial, according to the following criteria: random sequence; allocation concealment; blinding of the patient, healthcare professionals, outcome assessors, data collectors and data analysts; incomplete outcome data; selective outcome reporting; and major baseline imbalance. Reviewers gave response options of ‘definitely yes’, ‘probably yes’, ‘probably no’ and ‘definitely no’ for each of the domains, with ‘definitely yes’ and ‘probably yes’ ultimately being assigned a low risk of bias and ‘definitely no’ and ‘probably no’ a high risk of bias (AKL et al., 2012). Reviewers decided disagreements by discussion, and one arbitrator (LL) judged unresolved disagreements.

Possible explanations for heterogeneity included the following: doses (higher vs. lower) with an expected larger effect with higher doses, duration of the treatment (longer vs. shorter) with an expected larger effect with longer duration of the treatment; and the risk of bias, with an expected larger effect in trials at high or

unclear risk of bias versus trials at low risk of bias. We ranked heterogeneity associated with pooled effect estimates with the use of a χ^2 test and the I^2 statistic (HIGGINS; THOMPSON, 2002). The following heterogeneity was considered: 0 to 25% (low heterogeneity); 50% (moderate heterogeneity); and 75% (high heterogeneity) (HIGGINS et al., 2003).

Confidence in pooled estimates of effect

Were also independently will rate the quality of evidence from RCT for each of the outcomes by using GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (GUYATT et al., 2011). In the GRADE approach, randomized trials begin as high-quality evidence but may be rated down by one or more of five categories of limitations: risk of bias, inconsistency, indirectness, imprecision, and reporting bias.

Data synthesis

Analyses were conducted for each herbal intervention for each outcome of interest. Meta-analyses were conducted using Comprehensive Meta-Analysis STATA software (version 14.1). We used random effects meta-analyses (MONTORI et al., 2008), which are conservative in that they consider within-studies and between-studies differences in calculating the error term used in the analysis.

For trials that reported dichotomous outcomes, was calculated the pooled relative risk with associated 95% confidence interval (95%CI). For continuous outcomes, the studies that reported the same construct, using different measurement instruments, we calculated the SMD (standardized mean difference) that expresses the intervention effect in standard deviation units, rather than the original units of measurement, with the value of SMD depending on the size of the effect (the difference between means) and the standard deviation of the outcomes (the inherent variability among participants) (BUSSE et al., 2015).

Statistical approaches to enhance the interpretability of results of continuous outcomes outlined in this paragraph used methods cited as well as those described by Thorlund et al. (2011). Funnel plots were not created to explore possible

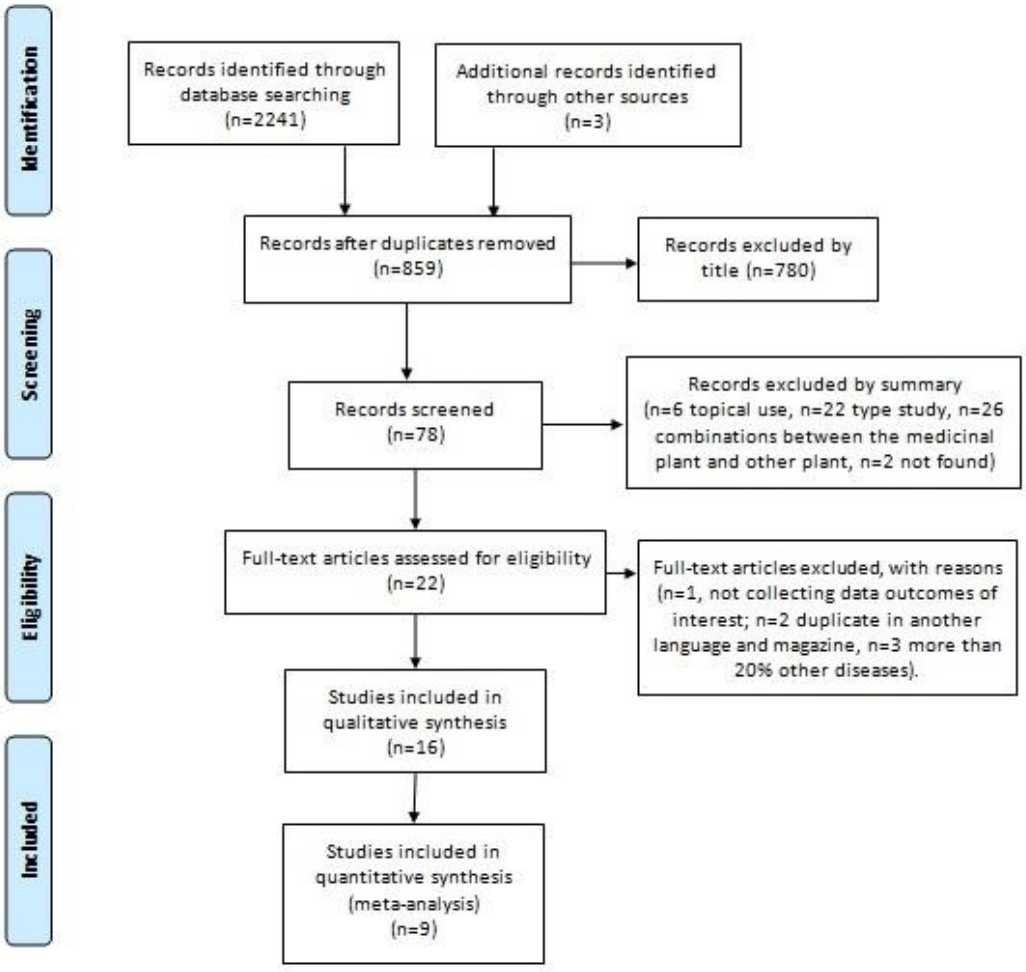
publication bias due to small number of studies. When the meta-analysis was not appropriated, we provided a narrative synthesis of studies.

Results

Literature search results

The search was conducted for each herbal medicine individually (appendixes A and B, respectively). A total of 2,241 publications were found, 1,385 remained after removing duplicates, 837 were excluded based on review of the title and abstract. Two studies (BILLER et al., 2002; FRERICK et al., 2001) for *H. procumbens* were excluded because the full text was not found despite of extensive search. From the 22 remaining articles, 16 fulfilled the inclusion criteria and 9 RCT were included in meta-analysis (Figure 1). The characteristics of the included studies are provided in appendix D.

Figure 1. Flowchart for literature search and study selection



Description of the studies

Sixteen RCT, involving 1,741 patients suffering from OA were included in this review. Most of them compared the intervention of herbal medicines to a placebo controlled (n=6) or active controlled study (n=5). Five studies compared the intervention of herbal medicine with placebo control and active control (in three or more groups). The included articles are related to seven of the thirteen herbal medicines studied: *B. serrata* (n=2), *C. longa* (or *C. domestica*) (n=3), *H. procumbens* (n=1), *S. daphnoides, S. purpurea* (n=3*), U. guianensis* (n=2), *Z. officinale* (n=5) (Appendixes E-M). The majority of the population (63%) presented OA in the knees (n=10). Patient follow-up took place between 14 and 180 days. Most of the studies used concomitant analgesic drug (n=11) and only two studies reported being financed by the pharmaceutical industry (Table 2). Only two studies did not use the

classification criteria organized by the American College of Rheumatology (ACR). The outcomes differ among the studies, which limited the use of some of them for meta-analysis.

Table 2. Characteristics of the included studies

CHARACTERISTICS	STUDIES	PATIENTS
Total number of patients	16	1,741
Female	16	74.3% (25.3% – 89.4%)
HERBAL MEDICINE (marker)		**Number of patients**
H. procumbens (Harpagoside)	1	122
U. guianensis (not known)	2	90
B. serrata (boswellic acid - AKBA*)*	2	96
C. longa (C. domestica) (Curcuminoids)	3	594
S. daphnoides, *S. purpurea* (Salicin)	3	265
Z. officinale (gingerols)	5	578
Clinical condition		**Number of patients**
Osteoarthritis knee	13	1,116
Osteoarthritis knee and hip	3	625
REGION		**Number of patients**
Asia	8	1,130
Germany	3	265
Other European countries	2	189
South America	2	90
Non-specified	1	71
FOLLOW-UP (in days)		
Average	16	56
Median (min –max)	16	42 (14 - 180)
USE OF CONCOMITANT MEDICATION		
Yes	12	
No	3	
Non-specified	1	
YEAR OF PUBLICATION		**Number of patients**
1997-2006	9	720
2007-2014	7	1,021
FUNDED BY THE INDUSTRY		**Number of patients**
Yes	2	138
Non-specified	14	1,562

Bias risk (Figure 2)

Only three studies (18.75%) adequately fulfilled all validation criteria and, thus presented minimum bias risk (SCHMID et al., 2001; WIGLER et al., 2003; BIEGERT et al., 2004).

Randomization and allocation

Nine (56.25%) studies did not report enough data about the randomization and allocation process to allow any assessment, presenting selection bias (BLIDDAL et al., 2000; CHANTRE et al., 2000; HAGHIGHI et al., 2005; KUPTNIRATSAIKUL et al., 2009; LARDOS et al., 2004; PARAMDEEP, 2013; PISCOYA, HERMAN, 1997; PISCOYA et al., 2001; ZAKERI et al., 2011). Other studies reported complete data regarding randomized sequence generation (table of randomized number or generation of numbers randomized with the use of computers and allocation informed by authors).

Blinding

Most of the studies (n=12) described the blinding of patient and healthcare professional (except SONTAKKE et al. (2007) and PARAMDEEP (2013)) due to the fact that they are open trials in which both the researches and the participants know which treatment is administered; and Madhu, Chanda and Saji (2013) and Kuptniratsaikul et al. (2009) that are single blind studies, where only the patient was blind for the intervention, were the ones that generated high risk detection bias.

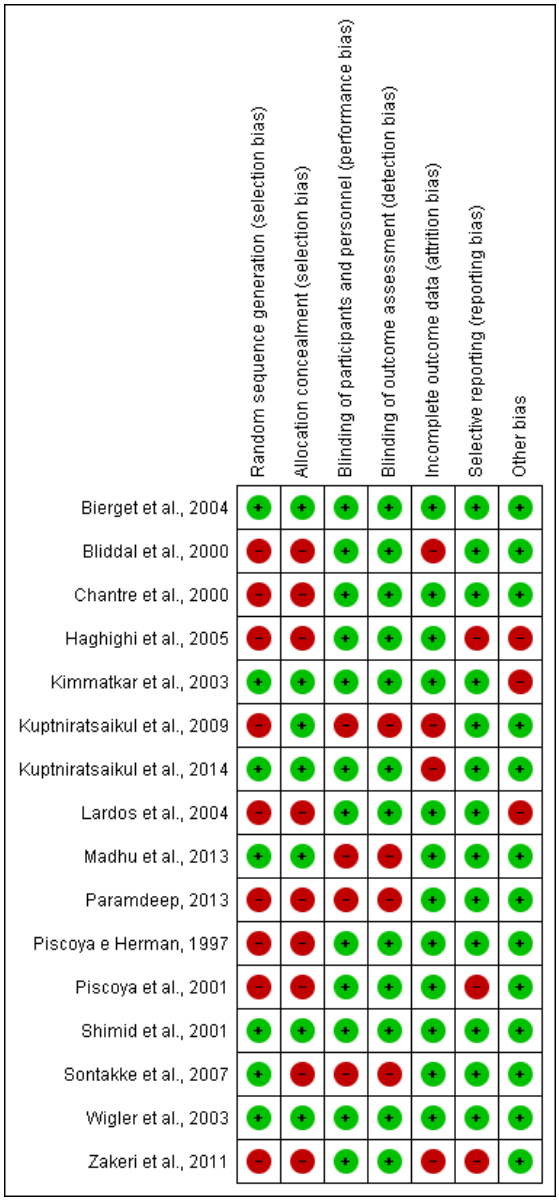
Outcomes

All authors reported whether there was loss of follow-up and/or patients exclusion during the study, explicitly and separately reported in the groups of the study. There was risk of attrition bias in four groups (BLIDDAL et al., 2000; KUPTNIRATSAIKUL et al., 2009; KUPTNIRATSAIKUL et al., 2014; ZAKERI et al., 2011) once they executed the simple input of lost data inappropriately (did not presented their results by intention of treatment) and did not discuss the implications of follow-up loss. Zakeri et al. (2011), Haghighi et al. (2005) and Piscoya et al. (2001) did not report adverse events and therefore, presented reporting bias.

Other sources of bias

Two studies related to the herbal medicine *Z. officinale* were financed by pharmaceutical companies (BLIDDAL et al., 2000; WIGLER et al., 2003). Three clinical trials did not use the classification criteria created by the ACR for OA diagnosis, producing doubts regarding the classification for inclusion of patients in the studies (LARDOS et al., 2004; HAGHIGHI et al., 2005; KIMMATKAR et al., 2003).

Figure 1. Consensus of the authors about bias risk for each study included.



Effect of the interventions

B. serrata

Two studies using *B. serrata* extract were included but meta-analysis not was conducted due to divergences in interventions. Kimmatkar et al. (2003) randomized 30 patients with knee OA (ACR criteria) into two groups and compared the effects of *B. serrata* (999mg/day) to placebo in a crossover study (three-week washout) during 8 weeks (data extracted for the first phase of the study only). After 8 weeks of treatment, *B. Serrata* was more effective for the outcome pain and physical function,

as well as for the reduction of the severity of the edema (p<0.001). The instrument for assessing pain was modified VAS with a score varying from 0 to 3 (0= no symptom, 1= mild symptom, 2= moderate symptom, 3= severe symptom). There was no follow-up loss and only two patients from the intervention group reported mild adverse events (nausea and epigastric pain).

Sontakke et al. (2007) compared *B. serrata* extract (999mg/day) to anti-inflammatory valdecoxib (10mg/day) in a group of 66 patients (33 patients in each group) with knee OA (ACR criteria) during a six-month treatment. The study reported follow-up loss and the statistical analysis were conducted with the use of ITT (Intention To Treat). This open trial results were favorable to the intervention with for the criteria pain, physical function and stiffness in WOMAC (even though it presented a slower onset) (p<0.001). Only one patient from the intervention group presented diarrhea as adverse event.

C. longa* (or *C. domestica)

The search found three RCT. Kuptniratsaikul et al. (2009) randomized 107 patients suffering from OA of the knee (ACR criteria) into two groups: *C. domestica* (n=52) receiving 2,000mg/day of the extract and ibuprofen (n=55) receiving 800mg/day for 42 weeks. Follow-up loss were reported by the authors and statistical analysis conducted per protocol. No statistically significant difference was found for the outcomes pain, except for pain on stairs (p<0.016) and physical function, suggesting that *C. domestica* extract has efficacy compared to ibuprofen to pain and function physical caused by OA. No statistically significant difference was found between the groups regarding adverse effects (p<0.36).

Kuptniratsaikul et al. (2014) in double blind study randomized of 367 patients suffering from OA of the knee (ACR criteria) compared the use of *C. domestica* extract (1,500mg/day) to ibuprofen (1,200mg/day) during four weeks. The comparison between the groups did not show significant differences in WOMAC score for pain, physical function and stiffness (p=0.531; p=0.278; p=0.522, respectively), and the number of individuals reporting adverse events between the groups did not differ (35.7% in ibuprofen and 29.7% in *C. domestica* group, p=0.222).

Madhu et al. (2007) compared four groups: *C. longa* extract (1,000mg/day), glucosamine (1,500mg/day), *C. longa* + glucosamine (1,000mg + 1,500mg) and

placebo. More pain reduction (VAS) was observed in patients that received *C. longa* and glucosamine alone when compared to placebo ($p<0.05$). The reduction in pain (WOMAC score) was significantly higher in the group for *C. longa* in comparison to placebo ($p=0.05$) e com *C. longa* + glucosamine ($p<0.05$) (Figure 3). The use of rescue medication was smaller in the group *C. longa* when compared to the other groups ($p<0.01$). A total of 13 adverse events was observed, the smaller number occurred in the group using herbal medicine. Once the author did not describe the number of patients (but the number of events) this study was not included in the meta-analysis.

Meta-analysis was conducted for the outcome pain and physical function (KUPTNIRATSAIKUL et al., 2009 and KUPTNIRATSAIKUL et al., 2014) comparing herbal medicine to ibuprofen. Ibuprofen group was similar plant for pain and physical function (Figures 3, 4). Herbal medicine was safer than ibuprofen (Figure 5).

Figure 3. Forest plot of meta-analysis for pain reduction of herbal medicines to treatment of OA.

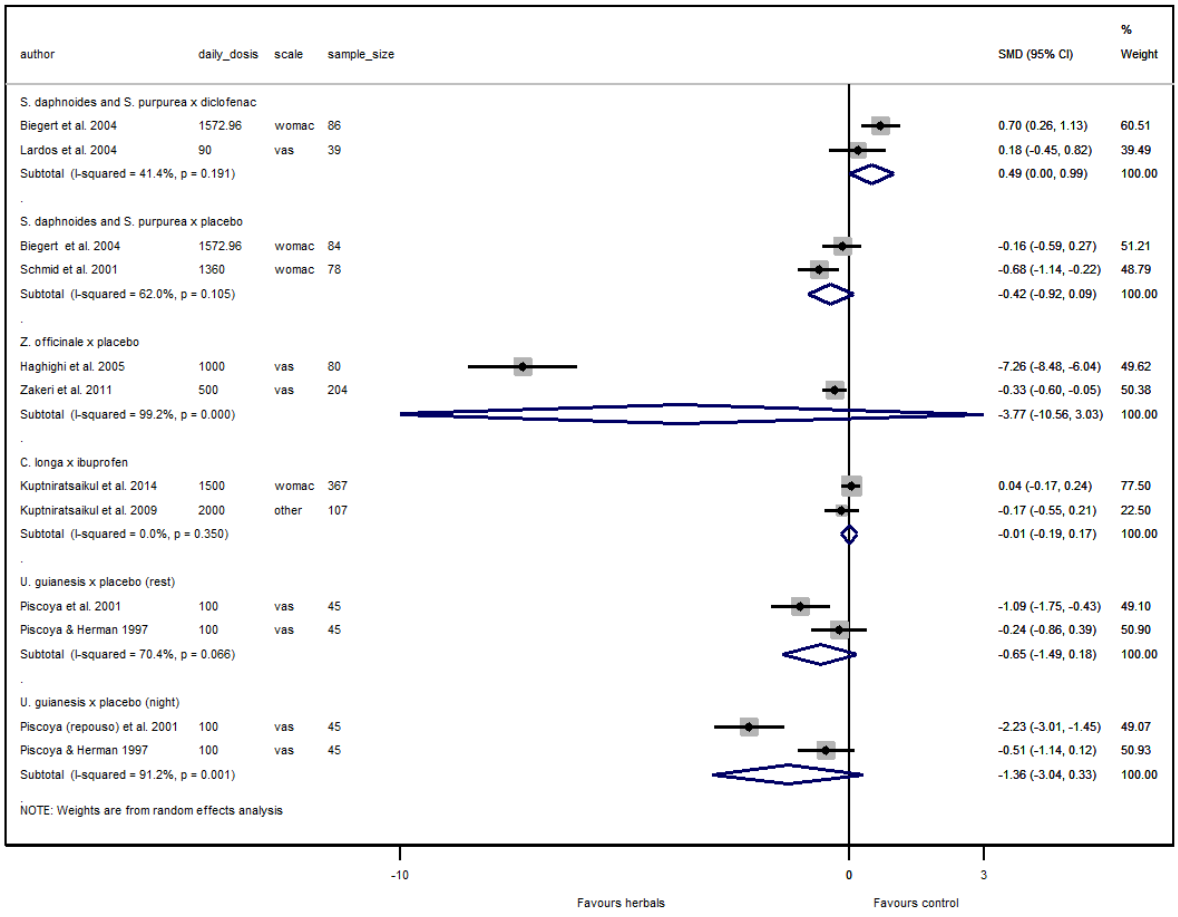


Figure 4. Forest plot of meta-analysis for improved physical function of herbal medicines to treatment of OA.

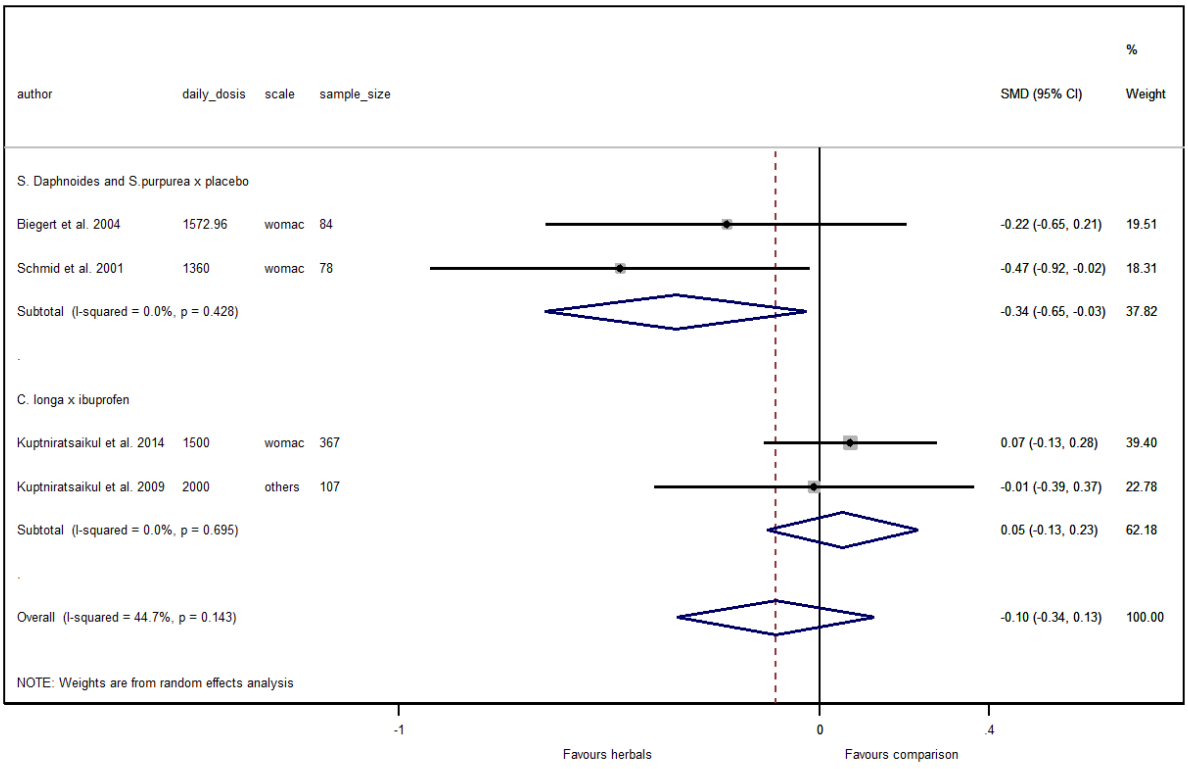
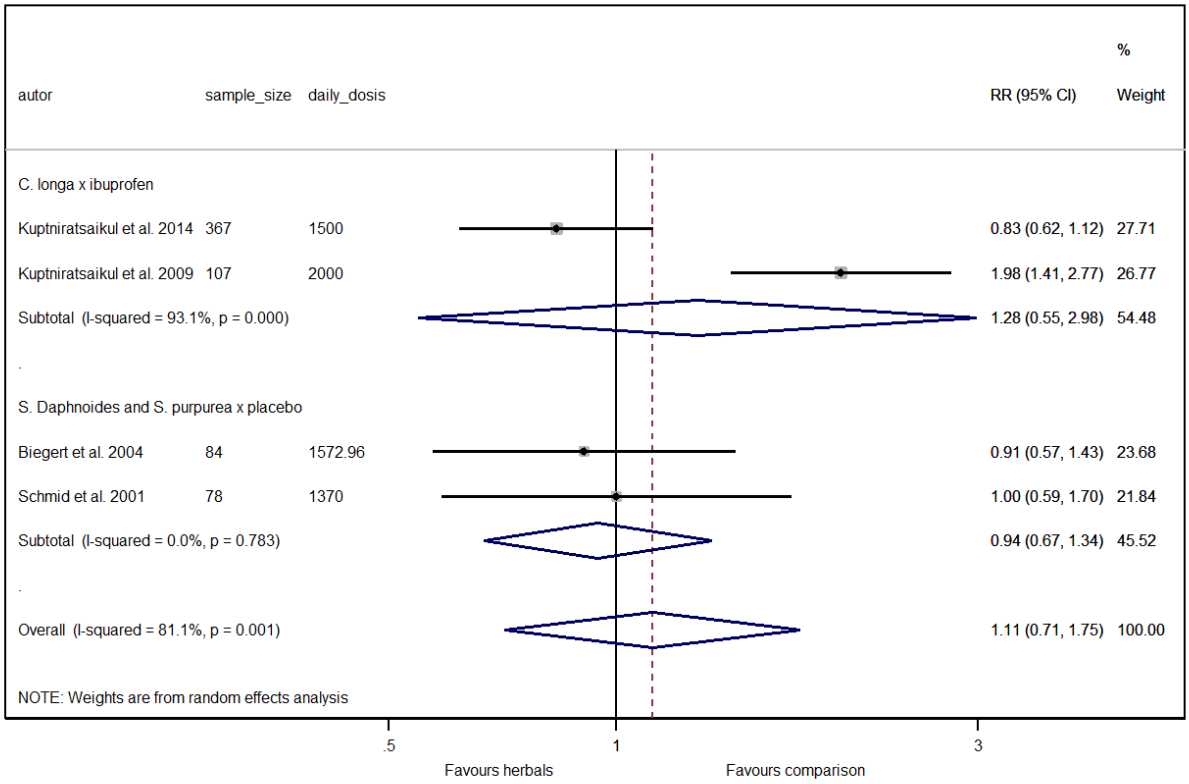


Figure 5. Forest plot of meta-analysis for adverse events of herbal medicines to treatment of OA.



H. procumbens

Only one study was found (CHANTRE et al., 2000) with a total of 122 patients suffering from OA in the knees (72.2%) or hips (27.8%) (ACR criteria) which were randomized into two groups: group that received herbal (n=62 patients) (435 mg/capsule of the extracted prepared from roots of *H. procumbens,* 6 capsules/day) and the group that received 100mg/day of diacerein (n=60 patients), both groups used the medication for 4 months. There were improvements in pain (with the use of VAS 0-100mm) (MD=-0.20, IC95%= -0.55 to 0.16) between the groups (p>0.05). The global assessment of the efficacy revealed similar results for both treatments, with 65.3% and 60% of the patients treated with the herbal medicine and the diacerein, respectively, assessed as having a positive result (very good or good). Regarding safety profile, 26 (43.3%) patients that had diacerein and 16 (25.8%) that had *H. Procumbens* presented adverse events, most of them gastrointestinal, which caused the exclusion of a higher number of participants from the diacerein group (n=14)

compared to the *H. Procumbens* group (n=8). Global evaluation of patient's tolerance was favorable to herbal medicine.

S. daphnoides* and *S. purpurea

Three studies were included. Schmid et al. (2001) randomized 78 patients suffering from OA of the knee or hips to receive de *S. purpurea* and *S. daphnoides* (daily dosage corresponding to 240mg/day of salicin) or placebo during 2 weeks (after 4 to 6 days of washout). Analgesic use was allowed at any period of the study. The outcome pain was favorable to the intervention group (WOMAC index) after two weeks of treatment (pain reduced in 14% with the use of the herbal medicine and increased by 2% in the placebo) (p=0.047). Physical function and stiffness were better in the intervention group, however, without statistical difference. The outcomes for pain and physical function in Schmid et al. (2001) were not presented with the standard deviation values, and then, we used the values of standard deviation of the baseline to include the study in the meta-analysis. There was no statistically significant difference between the groups regarding adverse events, 16 patients from each group reported such events and one patient presented severe allergy and abandoned the study after 14 days.

Another double blind randomized study (BIEGERT et al., 2004) compared the extract from *S. daphnoides* bark (equivalent to 240mg of salicin) to placebo and diclofenac (100mg) during a six-week treatment period in adult patients (n=127) suffering from OA of the knee or hips. The results showed no statistically significant difference in the reduction of WOMAC pain scores in groups. Physical function and stiffness showed significant improvement in the diclofenac group compared to the placebo group and the herbal medicine did not show any significant difference. Life quality index, SF-36 (36-Item Short Form Health Survey) was superior for diclofenac in relation to placebo. The number of adverse events was higher in the diclofenac group, mainly gastrointestinal ones (p=0.001) and a patient from this group experienced a severe adverse event and was removed from the study and admited to hospital for suspected gastritis and deep vein thrombosis.

Lardos et al. (2004) compared the use of willow bark (90mg of salicin/day) with willow bark (180mg of salicin/day) and diclofenac (150mg/day). 60 adult patients with OA of the knee and hips were randomized and assessed for six months. No other

drug was allowed during the period of the study. There was no significant difference regarding the outcome pain. The author did not report variance measures for the outcomes (improvement in global physical function and increased number of pain-free patients) and then the results were not included in meta-analysis. Only one patient from diclofenac group reported an adverse event to the treatment.

Meta-analysis perfomed with the studies Biegert et al. (2004) and Schmid et al. (2001) showed no benefit of the use of the herbal medicine for reducing pain and improving physical function compared to placebo (Figures 3, 4). Biegert et al. (2004) and Lardos et al. (2004) also did not show favorable results to the use of plant compared to diclofenac for pain outcome (Figure 3). Meta-analysis of adverse events show no significant difference between the herbal medicine and placebo (BIEGERT et al. (2004) and SCHMID et al. (2001)) (Figure 5).

U. guianensis

Two studies were found. Piscoya, Herman (1997) randomized 45 patients aiming to compare the use of *U. guianensis* extract to placebo for four weeks. The reduction in pain (during movement) was favorable to intervention group two weeks afer use of plant ($p<0.05$). There was a higher number of patients who had adverse events in the phytotherapy group (n=10) compared to placebo (n=3), but, the authors not performed statistical tests.

Piscoya et al. (2001) used patients with diagnosis for knee OA (ACR criteria) that were randomized to receive aqueous extract of *U. guianensis* (single daily oral 100mg dosage) (n=30 patients) or placebo (n=15 patients) for four weeks. There was a significant reduction of pain from the first week of the treatment with the herbal medicine. In the global evaluation of the disease, doctors and patients reported improvement only from the second week ($p<0.01$). Pain (at rest and night) did not present any statistically significant difference in relation to the placebo. This study did not report adverse events. Meta-analysis showed no benefit for the use of the *U. guianensis* in relation to placebo to reduce pain at rest and night (Figure 3).

Z. officinale

Five RCT were conducted. Haguigui et al. (2005) randomized 120 patients with OA of the knee and hip into 3 groups: *Z. officinale* (1,000mg capsule, equivalent to 30mg of the extract), ibuprofen (1,200mg) and placebo, in a 30-day treatment

period. Statistically significant difference was found for the outcome pain which benefit the herbal medicine compared to placebo ($p<0.001$), but no statistic difference in relation to ibuprofen ($p>0.05$). The study did not report any adverse events.

Wigler et al. (2003) randomized 29 patients with OA of the knee to receive *Z. officinale* extract 1,000mg (n=14) and placebo (n=15) for around 48 weeks. During the first 12 weeks, the differences between the groups were not statistically significant for the outcome pain (due to the fact that it was a crossover study, data were extracted only for the first phase of the study). The authors did not report standard deviation for pain measures, which did not allow its inclusion in meta-analysis. Only one adverse event (heartburn) was presented by a patient from *Z. officinale* group.

Bliddal et al. (2000) compared ginger extract (500mg/day) to placebo and ibuprofen (400mg/day) in patients with OA of the hips and knees in a double blind, controlled, crossover study (one week washout). Data were observed only in the first phase of the study. The outcome pain (VAS) decrease for all periods of the treatment; ibuprofen was superior to the herbal medicine and placebo ($p<0.05$). A total of 47 adverse events was registered in 34 patients (*Z. officinale* n=10, placebo n=9, ibuprofen n=15), but without significant differences.

Zakeri et al. (2011) randomized 204 patients with OA of the knee that receive 500mg/day of ginger extract (n=103) or placebo (n=101) for 6 weeks. After this period, pain reduction (VAS 0-100 mm) was significantly higher in the ginger group at rest (OR=1.76) as well as after a 50-meter walk (OR=2.05) ($p<0.05$). There was also improvement in the ginger group pain (OR=2.56), stiffness (OR=2.01) and physical function (OR=2.56) ($p<0.05$). The study did not report adverse events.

Paramdeep (2013) conducted an open trial study with 60 patients suffering from OA of the knee randomized into three groups: diclofenac 50mg + placebo (n=20), *Z. officinale* 750mg + placebo (n=20) e *Z. officinale* 750mg/day + diclofenac 50mg (n=20), for a 12-week period. The percentage of improvement for pain (WOMAC and VAS scales) was statistically significant for the group diclofenac 50mg + placebo compared to the herbal medicine 750mg + placebo ($p<0.05$). No difference was observed between the groups Z. *officinale* 750mg/day + placebo e *Z. officinale*

750mg/day + diclofenac 50 mg (p>0.05). Adverse events did not present differences among the groups (p>0.05).

Meta-analysis was performed for the outcome pain comparing the herbal medicine to placebo (HAGUIGUI et al., 2005; ZAKERI et al., 2011). The intervention group showed be more effective than placebo but presented high heterogeneity (Figure 3).

Discussion

This study evaluated the plants marked in Brazil for the treatment of OA and found clinical trials to 7 of 13 studied plants (*H. procumbens, B. serrata, U. guianensis, S. daphnoides* and *S. purpurea, C. longa* (or *C. domestica)* and *Z. officinale*). From a total of 16 studies, 9 were included in the meta-analysis (*U. guianensis* (n=2), *S. daphnoides* and *S. purpurea* (n=3), *C. longa (n=2)* and *Z. officinale* (n=2).

B. serrata (999mg daily dose in both studies) was more effective in reducing pain, stiffness, swelling, and improves physical function compared to placebo and valdecoxib. However, the duration of treatment differed between them (2 and 8 months (respectively, KIMMATKAR et al. (2003) and SONTAKKE et al. (2007)). Both studies reported mild adverse events (nausea and gastric distress) with the use of the plant, as also reported by Basch et al. (2004). The SR of Cameron et al. (2014) includes five studies of this plant; some of them were herbal medicines associations, and then were not included in our study. However, the findings of our study was similar to Cameron et al. (2014) since none RCT was published; indicating that the available evidence is not sufficient to confirm the benefit of using this phytotherapic.

C. longa extract was as effective as ibuprofen for the treatment of osteoarthritic pain and pain-related functional impairments, but it was considered more safe (KUPTNIRATSAIKUL et al., 2009; KUPTNIRATSAIKUL et al., 2014). While in vitro studies suggest that curcumin is an effective therapy for OA (JACKSON et al., 2006; LEV-ARI et al., 2006; MATHY-HARTERT et al., 2009), there are few RCT and most have weak methodological quality, this makes it impossible to confirm the findings. Two new studies were added since the last review (CAMERON et al.,

2014) and we observed similar efficacy from the plant in relation to ibuprofen for some of the outcomes assessed.

Regarding safety, NSAID can cause adverse events gastrointestinal such as peptic ulcers and subsequent risk of bleeding and perforation that may be significant for OA patients due to long use of those drugs (PEDDADA et al., 2015). These effects could be less observed with the use of Curcumin due to their selective inhibition of COX-2 (GOEL; BOLAND; CHAHAN, 2001).

Chantre et al. (2000) founded that *H. procumbens* was similarly to diacerhein in reducing pain, but allowed less usage of diclofenac and acetaminophen. Although of Cameron et al. (2014) have included two other studies (BILLER et al. 2002, FRERICK et al. 2001), which we not located the full text as previously described); the authors not performed the meta-analysis because of intervention differences found in clinical trials. Then, the evidence available continue not enought to confirm the efficacy and safety of this herbal medicine for OA.

Chantre et al. (2000) used daily dose of 57mg of marker harpagoside. This dose is in accordance with Gagnier; Chrubasik; Manheimer (2007) that suggested the daily dose of at least 50mg harpagoside; and with the European Pharmacopoeia which considers the dose of 50 to 100 mg harpagoside suitable for the treatment of OA. The safety profile was similar than placebo and showed no serious adverse events. This was also observed by Viachojannis and Chrubasik (2008) that evaluated 28 RCT and found no higher incidence of adverse events with this herbal medicine.

There was no benefit of *S. purpurea* (in the daily dose of 240 mg of salicin - active marker) to improve pain and physical function compared to placebo (BIEGERT et al., 2004; SCHMID et al., 2001); and also, there is no benefit to pain improvement compared to diclofenac (BIEGERT et al., 2004; LARDOS et al., 2004). The findings of our study differ from SR published previously, due to the inclusion of Lardos et al. (2004). We observed similarity in the use of herbal medicine compared to diclofenac in improvement of the patient's pain with OA. The number of adverse events did not differ with the use of this herbal compared to placebo (BIEGERT et al., 2004; SCHMID et al., 2001), but it was considered safer when compared to diclofenac (BIEGERT et al., 2004). Although this study not observed serious adverse events, a patient left the study because of allergic symptoms. According with Boullata,

McDonnel and Oliva (2003), most studies from this plant reported mild adverse events, however, it is important to reinforce that anaphylactic reactions may occur in patients with a history of allergy to salicylates, which contraindicate the usage of willow bark preparations in these patients.

The meta-analysis showed that the *U. guianensis* was more effective in pain reduction compared to placebo (PISCOYA; HERMAN, 1997; PISCOYA et al., 2001). The anti-inflammatory properties of this plant occur due to their ability to suppress the synthesis of TNFα (tumoral necrosis factor alpha) (SANDOVAL et al., 2000). Cameron et al. (2014) includes two studies on its SR one being mixture of plants. The study of Piscoya and Herman (1997) was not included in the Cochrane review and enabled us to verify the effectiveness of the plant to the outcome pain. Other efficacy outcomes were not assessed because the studies were not adequately reported.

Our results showed benefits from the use of *Z. officinalle* in relation to placebo in pain reduction (HAGHIGHI et al., 2005; ZAKERI et al., 2011). These studies were not included by Cameron et al. (2014). Although the results have shown the benefit of the herbal in reducing pain, there are few RCT and most of them presented selectivon bias, attrition bias and reporting bias. Therefore, well-designed trials are needed to elucidate the beneficial effects of ginger extract. The safety profile was similar between the plant, diclofenac and placebo.

Many of the results achieved in this study were inconclusive, once there was a small number of RCT evaluating the use of herbal medicines for AO. In addition, most of the RCT differed in relation to its design, interventions, dosage and duration of treatment, which compromised the meta-analysis for most outcomes assessed. The safety evaluation of the use of plants was also impaired, once some studies no reported adverse effects, generating an important reporting bias (PISCOYA et al., 2001; HAGHIGHI et al., 2005; ZAKERI et al., 2011).

It is important to note that the few adverse events reported were based on studies with limited treatment duration, and then the prolonged intake of herbal medicines was not evaluated. Another limitation of this study was the fact that some RCT had not report relevant outcomes to the patient, such as the quality of life and satisfaction with treatment.

Another point that should be highlighted is that the exact components of the tested plants can be uncertain since in most of the clinical trials, the preparations were produced exclusively for the study. The preparation of the plant was not discussed in some studies (BLIDDAL et al., 2000, KUPTNIRATSAIKUL et al., 2014, LARDOS et al., 2004, PARAMDEEP, 2013), although it was indicated the content of active compounds. The studies of Chantre et al. (2000), Madhu; Chanda; Saji, (2013), Sontakke et al. (2007) used industrial pharmaceutical products; while kimmatkar et al. (2003), Zakeri et al., 2011, Wigler et al., 2003 used products produced by pharmacies or by the institution where the research was conducted.

This systematic review evaluated the oral use of herbal medicines sold in Brazil for the OA and although some of these plants had already been evaluated in another published SR, this study provides updated information about them. We not found RCT to the plants *B. virgilioides*, *C. ambrosioides*, *C. curassavica* (or *C. verbenacea*), *P. gratissima* (or *P. americana*), *S. alba* and *U. tomentosa*. We found few clinical trials of *B. Serrata, C. longa* (or *C. domestica*) *H. procumbens, S. daphnoides, S. purpurea, U. guianensis* and *Z. officinale*, showing the necessity of more RCT to prove effectiveness and safety of these plants.

H. procumbens, *U. tomentosa* and *S. alba* are herbal medicines financed by the Ministry of Health and may be prescribed for SUS users, but they should not be recommended for the treatment of OA. Other five plants included in this review *C. longa (*or *C. domestica*)*, C. ambrosioides*, *C. curassavica* (or *C. verbenacea*), *Z. officinale* and *P. gratissima* (or *P. americana*) are part of the RENISUS and are considered plants with potential to generate SUS interest products. *B. serrata*, *B. virgilioides*, *S. daphnoides, S. purpurea* and *U. guianensis* are not financed by Brazilian government and not belongs to RENISUS, however are available in the trade and are being used by the Brazilian population.

None of the studies found was conducted in Brazil. The use of those plants are based only on traditional use; thus, it is needed to encourage clinical research in Brazil to assess the benefits and safety in the use of these herbal medicines. It is important that the Brazilian government is aware of the phytotherapic of financing for use these phytotherapics in the public health system. Of the 16 plants studied, only three (*C. longa* or *C. domestica, U. guianensis* and *Z. officinale)* showed benefit to

some outcome evaluated, however, these results were based in few articles with methodological problems and some theirs no reported adverse events. The results of this systematic review may assist prescribers in decision making for clinical practice and help patients look out for more effective and safer treatments for the symptoms of OA.

Conclusions

The results of this study should be interpreted with care due to low number of included studies, which limits the findings. Furthermore, the heterogeneity observed in the studies with relation to dose, duration of treatment and the risk of bias committed the analysis of the effectiveness and safety of herbal medicines. The evidence was not sufficient to support the safe and effective use of these herbal medicines to OA. Thus, this study guides managers of the Brazilian public health system and prescribers in the decision making regarding the use of these herbal medicines to OA.

Competing interests

The authors declare no conflict of interest.

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CONSIDERAÇÕES FINAIS

Este estudo avaliou a efetividade e segurança dos medicamentos de uso oral à base de plantas medicinais comercializados no Brasil para o tratamento da OA. A heterogeneidade observada nos estudos com relação à dose, duração do tratamento e o risco de viés comprometeu a análise da eficácia e segurança dos medicamentos à base de plantas.

Das 16 plantas estudadas, apenas três (*C. longa* ou *C. domestica*, *U. guianensis* e *Z. officinale*) mostraram algum benefício, no entanto, esses resultados foram baseados em poucos artigos. Desta forma, a evidência não foi suficiente para apoiar o uso seguro e eficaz destes medicamentos à base de plantas para OA. Estes resultados podem orientar gestores do sistema público de saúde brasileiro e prescritores na tomada de decisão quanto à utilização destes medicamentos à base de plantas para OA

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ANEXO A: ORIENTAÇÕES PARA APRESENTAÇÃO DE DISSERTAÇÕES DO PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS FARMACÊUTICAS DA UNIVERSIDADE DE SOROCABA

Orientações para apresentação de dissertações do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba

As dissertações de mestrado do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba (PPGCF-Uniso) poderão ser apresentadas em dois formatos: o tradicional ou em formato de artigo(s) científico(s). Os trabalhos de investigação que possam resultar em patentes poderão ser apresentados na forma convencional, a critério do grupo de pesquisadores envolvidos, reservadas as particularidades exigidas em relação ao sigilo.

O formato tradicional segue o padrão descrito nas normas do "Manual para normalização de trabalhos acadêmicos" da Universidade de Sorocaba.

As dissertações entregues no formato de artigo científico têm como exigência a publicação ou, no mínimo, a submissão prévia de pelo menos um artigo em revista científica com classificação mínima Qualis/Capes B2 (de acordo com a categorização da WebQualis mais recente, na data do envio/publicação) e podem ser inseridos no idioma e na formatação estabelecida pelo(s) respectivo(s) periódico(s). Os demais artigos podem não ter sido submetidos ainda.

A dissertação no formato de artigo(s) científico(s) deverá possuir os elementos apresentados no Quadro 1.

Quadro 1 - Elementos para a construção da dissertação no formato de artigo(s) científico(s).

Elementos pré-textuais	*1. Folha de rosto*
	2. Errata (Opcional)
	3. Folha de aprovação
	4. Dedicatória (Opcional)
	5. Agradecimentos (Opcional)
	6. Epígrafe (Opcional)
	7. Resumo na língua vernácula
	8. Resumo em inglês (Abstract)
	9. Lista de abreviaturas e siglas; lista de tabelas e lista de símbolos (opcionais). Estas listas não devem conter as informações apresentadas nos artigos científicos.
	10. Sumário

Elementos textuais	*11. Introdução ou apresentação:* trata-se da parte inicial do texto com formulação clara e simples do tema investigado, constando a delimitação do assunto tratado, sua relevância e justificativa.
	12. Revisão de literatura: quando a revisão de literatura for concebida como artigo de revisão, este item deverá ser incluído no item resultado(s).
	13. Objetivos: geral e específico
	14. Material e Métodos (opcional). Quando parte dos resultados não for apresentada no formato de artigo, este item deverá ser incluído após os objetivos específicos. Quando o autor quiser apresentar o(s) método(s) de forma mais detalhada do que no artigo, este item pode também ser apresentado em separado.
	15. Resultados (pode ser apresentado no formato de artigos): deve(m) ser inserida(s) a(s) cópia(s) de artigo(s) derivado(s) da dissertação, previamente publicados, submetidos ou não para publicação em revistas científicas. Sugere-se que cada artigo seja antecedido de uma breve apresentação seguida dos elementos de identificação do artigo (autores, título, revista de publicação, volume, páginas). Os artigos anexados poderão ser apresentados nos formatos exigidos pelas revistas, as quais os artigos foram publicados e/ou submetidos. Parte dos resultados pode ser apresentada em separado dos artigos, quando conveniente.
	16. Discussão (opcional): O autor pode ampliar a discussão dos resultados, quando conveniente.
	17. Conclusão ou Considerações finais: esta parte deverá conter a conclusão do trabalho ou as considerações do autor sobre os resultados alcançados frente aos objetivos propostos.
Elementos pós-textuais	*18. Referências:* Devem seguir as normas do “Manual para normalização de trabalhos acadêmicos” da Universidade de Sorocaba. Não devem ser inseridas as referências apresentadas nos artigos.
	19. Apêndices (Opcional)
	20. Anexos (Opcional)

Encaminhamentos posteriores à defesa da dissertação:

1. A incorporação de correções e alterações sugeridas pela banca no artigo científico deve ser definida pelo orientador e informada ao mestrando;

2. O orientador continua sendo o responsável por aprovar a versão final do trabalho;

3. O trabalho final deve ser entregue na Secretaria da Pós-Graduação, impresso e acompanhado do arquivo digital em pdf (CD);

4. O arquivo digital (em pdf) deve conter o trabalho completo em único arquivo (incluindo capa, elementos pré-textuais, ficha catalográfica e folha de aprovação assinada por todos os membros da banca e demais seções).

4. Um dos exemplares impressos será encaminhado imediatamente à biblioteca, exceto quando for objeto de patente. Neste caso, os procedimentos devem ser discutidos previamente com a coordenação do programa;

5. Dissertações no formato de artigos podem não ser divulgadas imediatamente no site do programa, caso solicitado pelo orientador. Neste caso, apenas o resumo e o abstract serão divulgados no site, junto com a seguinte informação: ***Trabalho completo contendo artigos científicos. Aguardando a publicação dos resultados.***

6. A princípio, a versão eletrônica da dissertação contendo artigos poderá ser retida por até 12 meses. A partir deste prazo, o trabalho completo será divulgado na página do programa. Havendo necessidade de prorrogação dos 12 meses, o orientador deve discutir com a coordenação os encaminhamentos.

7. Os docentes devem informar à Secretaria do Programa (com cópia para a coordenação do programa), sempre que um artigo derivado de dissertação for publicado, acompanhado da referência no formato ABNT. Neste caso, será incluída no site a referência e um hiperlink para acesso do artigo, logo abaixo do resumo.

APÊNDICE A – PROTOCOLO DO ESTUDO

Título: Brazilian Oral Herbal Medication for Osteoarthritis: A Systematic Review Protocol

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Abstract

Background: Osteoarthritis affects 1% of the world's population and is the most common cause of musculoskeletal impairment in the elderly. Herbal medications are commonly used in Brazil to manage symptoms associated with osteoarthritis and some of them are financed by Brazilian government, however, the effectiveness of most of these agents is uncertain. The aim was to systematically review the efficacy and safety of 13 oral herbal medications used in Brazil for the treatment of osteoarthritis.

Methods: Randomized clinical trials eligible for our systematic review will enroll adults with osteoarthritis treated by a Brazilian herbal medication or a control group (placebo or active control). Using terms to include all forms of osteoarthritis combined with herbal medications, we will search the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; CINAHL; Web of Science; Health Star; AMED, the database of the Cochrane Complementary Medicine Field, LILACS; CAB abstracts, Clinical trial.gov, WHO trials registry, and Bank of Brazil Thesis (CAPES), to 31st January 2016, without restrictions concerning to language or status of publication. Outcomes of interest include the following: symptom relief (e.g. pain), adverse events (gastrointestinal bleeding, epigastric pain, nausea, and allergic reactions), discontinuation due to adverse events, quality of life and the satisfaction with the treatment. Dichotomous data will be summarized as risk ratios; continuous data will be given as standard average differences with 95% confidence intervals. A team of reviewers will assess each citation independently for eligibility and in duplicate it. For eligible studies, the same reviewers will perform data extraction, bias risk assessment, and determination of the overall quality of evidence for each of the outcomes using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) classification system.

Discussion: This is the first study that will evaluate the use herbal medications used in Brazil to the treatment of pain caused by osteoarthritis. The results could guide prescribers in decision-making in clinical practice, to inform the patients with pain caused by osteoarthritis in relation to effective and safe treatment options, and to inform the managers of the public health system which of them plants could actually be financed by the Brazilian government.

Systematic review registration: PROSPERO 42015019793. (http://www.crd.york.ac.uk/PROSPERO/).

Background

Osteoarthritis is the most common musculoskeletal disease and is associated with significant functional decline and reduced quality of life [1]. It is characterized by loss of articular cartilage, subchondral bone remodeling, bone spurs, ligament laxity, weakening of the periarticular muscles, and thickening of the capsule and synovial membrane [2-4]. Osteoarthritis is the result of both mechanical and biological events that cause imbalance in the normal process of degradation and synthesis of joint cartilage chondrocyte, extracellular matrix, and subchondral bone [5].

The World Health Organization (WHO) states that osteoarthritis is a disease related to an aging population [6] and the leading cause of chronic disability in middle-aged and older populations [7]. The risk of osteoarthritis increases from 1% in 30-years old people to almost 10% in people over the age of 40 years and 50% in people over the age of 60 years [8]. Osteoarthritis produces a variety of serious social problems, both health and economic and is one of the more debilitating musculoskeletal diseases among the elderly [9].

Osteoarthritis can be associated with pain, stiffness and functional limitations [10-12]. It is estimated to affect 10% of men and 18% of women and occurs most often in the hip and knee [13].

Although treatment guidelines recommend analgesics as first-line drugs, the non-steroidal anti-inflammatory drugs are preferred, although they are less safe and more expensive [14]. Due to the high incidence of adverse events related to non-steroidal anti-inflammatory drugs (NSAID) and the high costs associated with adverse events (e.g., gastrointestinal bleeding or perforation, additional medical visits, diagnostic procedures, treatments and hospitalizations), therapeutic alternatives are an area of great interest [15-16].

The use of herbal medicines worldwide is substantial and increasing. In 2001 the United States, around 38% of adults and 12% of children report use of herbal medicine [17]. Use of herbal medicines in developing countries is even greater, and an estimated 85% of the Brazilian population use plants or preparations of these for

their healthcare [18]. In 2011, the Brazilian herbal market generated 1.1 billion in revenue, which included sales of 43 million units of phytomedicines [19].

In primary health care, the use of medicinal plants has been stimulated by guidelines from various national health conferences and by the WHO [20]. The National Policy of Integrative and Complementary Practices and the National Policy of Medicinal and Phytotherapeutic Plants adopted in 2006 were created to meet the demands of the Brazilian population. These policies were decisive steps towards introducing the use of medicinal and phytotherapeutic plants in the Brazilian Unified Health System (SUS) [21].

In Brazil, there are 13 herbal medications marketed for treatment of osteoarthritis: *Harpagophytum procumbens* DC. ex Meisn*., Uncaria tomentosa (Willd.)* DC., *Salix alba L.,* (financed by government), *Boswellia serrata* Roxb. ex Colebr., *Bowdichia virgilioides* Kunth., *Curcuma longa L*. (or *Curcuma domestica* Valeton*), Chenopodium ambrosioides* L., *Cordia curassavica (*Jacq.) Roem. & Schult. (or *Cordia verbenacea* DC.), *Salix daphnoides Vill, Salix purpurea L., Persea* gratissima Gaertn.f. (or *Persea americana* Mill.), *Uncaria guianensis* (Aubl.) J.F. Gmel and *Zingiber officinale* Roscoe.

Two systematic reviews evaluated the use of herbal medicines for the treatment of osteoarthritis by topical and oral use, respectively [22, 23]. However, these studies did not include some of the plants marketed in Brazil: *Bowdichia virgilioides* Kunth, *Chenopodium ambrosioides* L, *Cordia curassavica* (Jacq.) Roem. & Schult, *Salix alba* L. and *Uncaria tomentosa* (Willd.) DC. Of these plants, *Uncaria tomentosa* (Willd.) DC. and *Salix alba* L. are funded by Brazilian government to use in Unified Health System (SUS) and *Chenopodium ambrosioides* L. and *Cordia curassavica* (Jacq.) Roem. & Schult are part of a list of plants of interest for development of research in order to include them as medicines financed by SUS.

Despite the common use of herbal medicines for managing osteoarthritis in adults, the safety and efficacy of some of these agents are uncertain. We therefore conducted a systematic review of randomized controlled trials, which made use of oral herbal medicines used in Brazil for the treatment of osteoarthritis.

Methods

Standards

The systematic review will be performed according to the recommendations specified in the Cochrane Handbook for Interventional Reviews and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [24] (see additional file 1).

Protocol and Registration

We registered our review protocol in the International Prospective Register of Systematic Reviews (PROSPERO-CRD42015019793 - http://www.crd.york.ac.uk/PROSPERO/).

Eligibility criteria

Inclusion criteria

Patients: Adults (>18 years old) with a diagnosis of osteoarthritis according to the criteria of American College of Rheumatology (ACR): Western Ontario and McMaster Universities (WOMAC) [25] or the equivalent criterion of European League Against Rheumatism (EULAR): Lequesne index [26].

Interventions: One of the 13 oral herbal medicines used by Brazilian population from any of the following plant preparations (whole, powder, extract, crude drug, standardised mixture and drug extract ratio and solvent): *Boswellia serrata* Roxb. ex Colebr., *Bowdichia virgilioides* Kunth., *Curcuma longa* L. (or *Curcuma domestica* Valeton), *Chenopodium ambrosioides* L., *Cordia curassavica (*Jacq.) Roem. & Schult. (or *Cordia verbenacea* DC.), *Harpagophytum procumbens* DC. ex Meisn., *Persea* gratissima Gaertn.f. (or *Persea americana* Mill.), *Salix alba* L., *Salix daphnoides* Vill, *Salix purpurea* L., *Uncaria tomentosa* (Willd.) DC., *Uncaria guianensis* (Aubl.) J.F. Gmel and *Zingiber officinale* Roscoe. We will identify the daily dose, the active principles and the marker substance of each plant. We will also investigate if each herbal medicine was prepared according to the WHO recommendations for the manufacturing procedure of medicinal plant parts (http://apps.who.int/medicinedocs/en/d/Jh2984e/).

Type of study: Randomized Controlled Trials including a group in which patients received one of the herbal medications listed above compared to a control

group in which patients receive placebo or a non-herbal medicine controls (for example, NSAID).

Exclusion criteria

Patients: Studies in which more than 20% of patients have other associated disease.

Interventions: Studies that investigated the simultaneous use of more than one of the eligible plants will be excluded.

Measure outcomes

Our outcomes will be consistent with those proposed by the Cochrane Musculoskeletal Group systematic intervention reviews for osteoarthritis [27]. When necessary, the results will be evaluated to unification of the different scales.

Primary outcomes:

- pain in overall or on walking (Visual Analogue Scale – VAS, pain scale sub WOMAC; and other scales);
- physical function - global disability or walking disability (sub function range of WOMAC index and other scales);
- swelling (VAS and other scales);
- stiffness (WOMAC index and other scales);
- quality of life (Short Form-36 and other scales);

Secondary outcomes:

- adverse events: withdrawals and serious adverse events (that cause death, life-threatening, hospitalization, disability or permanent damage);
- number of patients reporting any adverse effects,
- activity limitations;
- satisfaction with the treatment;
- consume of rescue medication;
- duration of symptom resolved;

- change in the structure of the joint (according to American College of Rheumatology criteria for osteoarthritis classification).

Search methods for primary studies

Electronic searches

We will search the following electronic databases without language restrictions: the Cochrane Central Register of Controlled Trials (CENTRAL) part of The Cochrane Library, MEDLINE, EMBASE, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Web of Science, Health Star (via OVID), AMED, LILACS, CAB abstracts, clinical trial.gov, the WHO Trial Register and the Brazilian thesis database (CAPES), and trial register in Brazil (REBEC) to 31January 2016; without language and status of publication restrictions. We will combine terms that describe osteoarthritis and herbal medications, individually.

Searching other resources

We will review the reference list of every eligible study we identify and relevant review articles for additional eligible trials. We will write to the authors of all eligible trials and the pharmaceutical companies involved in the production of herbal medicines and inquire about additional trials of which they are aware. Five Brazilian scientific journals will also be searched by hand for additional eligible studies (Journal of Basic and Applied Pharmaceutical Sciences, Brazilian Journal of Pharmacy, Brazilian Journal of Pharmacognosy, Brazilian Journal of Medicinal Plants and Brazilian Journal of Pharmaceutical Sciences). Unpublished studies will be identified by searching in reference lists reported in the Brazilian legislation and conference proceedings (Medicinal Symposium of Brazilian medicinal plants; International Congress of Ethnopharmacology).

Search strategy

The search will be conducted individually for each plant. We will use the following Mesh terms: 1) intervention (scientific name of plant, synonymies of each medicinal plant; popular name of each medicinal plant); 2) Condition (osteoarthritis, ostepathritis, osteoarthritides, osteoarthrosis, osteoarthroses, arthritis, degenerative,

arthritides, degenerative, degenerative arthritides, degenerative arthritis and osteoarthrosis deformans). We will adapt the search strategy for each database. MEDLINE search strategy is provided in box 1.

Eligibility determination

Four reviewers (CC, MG, MB and SK), working in pairs, will independently screen potentially relevant citations and abstracts and will apply the selection criteria. We will obtain full texts of all articles that either reviewer feels might be eligible. Two reviewers will independently assess the eligibility of each full-text article and resolve disagreements by consensus. In case of duplicate publication, we will use the article with the more complete data.

Data extraction

Four reviewers (CC, MG, MB and SK), working in pairs, will independently extract the data and will record information regarding patients, methods, interventions, outcomes, and missing outcome data using standardized and pretested data extraction forms with instructions. Before starting data abstraction, we will conduct calibration exercises to ensure consistency between reviewers. We will contact study authors to resolve any uncertainties. Disagreements will be resolved by consensus with any unresolved issues referred to another reviewer.

Risk of bias in individual studies

Using a modified version of the Cochrane collaboration risk of bias tool [28-29] the same pairs of reviewers will independently asses the risk of bias for each randomized trial, according to the following criteria: random sequence; allocation concealment; blinding of the patient, healthcare professionals, outcome assessors, data collectors and data analysts; incomplete outcome data; selective outcome reporting; and major baseline imbalance. Reviewers will assign response options of ‘definitely yes’, ‘probably yes’, ‘probably no’ and ‘definitely no’ for each of the domains, with ‘definitely yes’ and ‘probably yes’ ultimately being assigned a low risk of bias and ‘definitely no’ and ‘probably no’ a high risk of Bias [30]. Reviewers will

resolve disagreements by discussion, and one arbitrator (LL) will adjudicate unresolved disagreements.

Possible explanations for heterogeneity will include the following: doses (higher vs. lower) with an expected larger effect with higher doses, duration of the treatment (longer vs. shorter) with an expected larger effect with longer duration of the treatment; and the risk of bias, with an expected larger effect in trials at high or unclear risk of bias versus trials at low risk of bias. We will assess heterogeneity associated with pooled effect estimates with the use of a χ^2 test and the I^2 statistic [31]. The following heterogeneity will be considered: 0 to 40% (no important heterogeneity); 30% to 60% (moderate heterogeneity); 50% to 90% (substantial heterogeneity); and 75% to 100% (considerable heterogeneity).

Confidence in pooled estimates of effect

We will also independently rate the quality of evidence from randomized trials for each of the outcomes by using GRADE approach [32-33]. In the GRADE approach, randomized trials begin as high-quality evidence but may be rated down by one or more of five categories of limitations: risk of bias, inconsistency, indirectness, imprecision, and reporting bias.

To measure agreement between the examiners, we will use the kappa statistics. Values of kappa between 0.40 and 0.59 have been considered to reflect fair agreement, values between 0.60 and 0.80 reflect good agreement, and values that are 0.75 or more reflect excellent agreement [34].

Data synthesis

We will conduct analyses for each herbal intervention and pool of them for each outcome of interest. We will determine the confidence in estimates for each body of evidence and conduct an analysis for the body of evidence that warrants greater confidence. If the two bodies of evidence warrant similar confidence, we will conduct analyses for both bodies of evidence.

Meta-analyses will be conducted using Comprehensive Meta-Analysis STATA software (version 10.1). We will use random effects meta-analyses [35], which are conservative in that they consider within-studies and between-studies differences in

calculating the error term used in the analysis. For trials that report dichotomous outcomes, we will calculate the pooled relative risk with associated 95% confidence interval (95%CI).

For continuous outcomes, e.g. pain score, function score, we will use weighted mean differences (WMD) and its 95%CI as effect measure after we convert them into same scale of Western Ontario and McMaster Universities osteoarthritis index (WOMAC) pain score (0-100) and function score (0-100), in which high score indicates worse outcome. For quality of life, we will convert different scales to SF-36, in which high scores indicate better outcome. Once the WMD has been calculated, we will contextualize this value by noting, when available, the corresponding anchor-based minimally important difference (MID), the smallest change in instrument score that patients perceive is important.

If studies reported the same construct using different measurement instruments, we will calculate the standardized mean difference (SMD) as sensitivity analysis. The SMD expresses the intervention effect in standard deviation units, rather than the original units of measurement, with the value of an SMD depending on the size of the effect (the difference between means) and the standard deviation of the outcomes (the inherent variability among participants). For outcome measures that have an established anchor-based MID, we will use this measure to convert the SMD into an odds ratio and risk difference [36].

To facilitate the interpretation of the effects of continuous outcomes, we will substitute the MID, when MID is available for different scales, for the standard deviation (denominator) in the SMD equation, which will result in more readily interpretable MID units instead of standard deviation units [37]. If an estimate of the MID is not available, we will use a statistical approach developed by Suissa [36] to provide a summary estimate of the proportion of patients who benefit from treatment across all studies. Statistical approaches to enhance the interpretability of results of continuous outcomes outlined in this paragraph will use methods cited as well as those described by Thorlund et al [39]. Funnel plots will be created to explore possible publication bias when at least 10 studies have contributed to a pooled analysis.

We will use recently developed approaches to address missing participant data for dichotomous outcomes [40] and continuous outcomes [41]. We will only apply these approaches to outcomes that meet the following criteria: show a significant treatment effect and report sufficient missing participant data to potentially introduce clinically important bias. Thresholds for important missing participant data will be determined on an outcome-by-outcome basis.

If sufficient studies are available, we will undertake subgroup analyses for doses (lower versus higher dose) and risk of bias (lower versus higher risk of bias). However, if the meta-analysis is not appropriate due to excessive heterogeneity of population, intervention, comparator, outcome, or methodology; we will construct summary tables and provide a narrative synthesis.

Summarizing evidence

We will present results in evidence profiles as recommended by the GRADE Working Group [42-43]. Evidence profiles provide succinct, easily digestible presentations of quality of evidence and magnitude of effects. Our evidence profiles will be constructed with the help of a software program, GRADEpro (http://ims.cochrane.org/gradepro) to include the following seven elements: (1) a list of until seven important outcomes, both desirable and undesirable; (2) a measure of the typical burden of these outcomes (e.g., control group, estimated risk); (3) a measure of the difference between risks with and without intervention; (4) the relative magnitude of effect; (5) numbers of participants and studies addressing these outcomes, as well as follow-up time; (6) a rating of the overall confidence in the estimate of effect for each outcome and (7) comments, which will include the MID if available.

Discussion

Our review will evaluate the available evidence for 13 oral Brazilian herbal interventions for osteoarthritis, provide estimates of the effectiveness of treatments and their associated harms, and evaluate the quality of the evidence in a thorough and consistent manner using the GRADE approach [44].

Previous systematic review had evaluated the oral use of herbal medicines to osteoarthritis [23]; however, five plants found in Brazilian market were not part of this review: *Bowdichia virgilioides* Kunth, *Chenopodium ambrosioides* L, *Cordia curassavica* (Jacq.) Roem. & Schult, *Salix alba* L. and *Uncaria tomentosa* (Willd.) DC; and the last two are financed by the Brazilian government. Despite the common use of oral herbal medications to manage osteoarthritis, these agents' safety and effectiveness are uncertain.

We therefore we will conduct a systematic review of these herbal medications used in Brazil for the treatment of osteoarthritis in order to guide prescribers in decision-making in clinical practice and to inform managers of the public health system which of these plants could actually be funded by the Brazilian government. The physician should opt for medication whose evidence is determined with the highest levels of quality in relation to effectiveness and safety. The results of our systematic review will be of interest for the public health system and practitioners worldwide, particularly in Brazil.

The compiled information about these herbal medications will inform patients and healthcare practitioners about their effectiveness and safety, and help facilitate evidence-based shared care decision-making. The evidence of this study will allow health professionals to be aware of the effectiveness and safety of herbal medications used in Brazil for the treatment of osteoarthritis. This study will also identify key areas for future research.

Abbreviations

Bank of Brazilian Thesis (CAPES), Grading of Recommendations Assessment, Development and Evaluation (GRADE), non-steroidal anti-inflammatory drugs (NSAID), Brazilian Unified Health System (SUS), Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), American College of Rheumatology (ACR), Western Ontario and McMaster Universities (WOMAC), European League Against Rheumatism (EULAR), Visual Analogue Scale (VAS), Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (Cumulative Index to Nursing and Allied Health Literature), 95% confidence interval (95%CI),

weighted mean differences (WMD), minimally important difference (MID) and standardized mean difference (SMD).

Competing interests

The authors declare that they have no competing interests.

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Authors contributions

CCB is the principal investigator, led the writing of the manuscript and will participate in data extraction. MDG is the project managers, co-investigator, contributed to the writing and revision of the protocol and will participate in data extraction. LCL is the project managers, co-investigator and drafted the manuscript. MWB is co-investigator, helped to revise the protocol and will participate in data extraction. JWB is co-investigator and helped to draft the protocol. SAK contributed to the writing and revision of the manuscript and will participate in data extraction. LW contributed to the writing and revision of protocol and will do statistical analysis. NB is responsible for search strategy and contributed to the writing of protocol.

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Box 1. Search strategy for Harpagophytum procumbens DC. ex Meisn. by MEDLINE (Via Ovid)

- #1 exp Osteoarthritis/ or Osteoarthrits.mp. (57958)
- #2 Osteoarthritides.mp. or exp Osteoarthritis/ (44712)
- #3 Osteoarthrosis.mp. or exp Osteoarthritis/ (45663)
- #4 Osteoarthroses.mp. or exp Osteoarthritis/ (44719)

- #5 Arthritis, Degenerative.mp. or exp Osteoarthritis/ (44737)
- #6 Arthritides, Degenerative.mp. or exp Osteoarthritis/ (44711)

- #7 Degenerative Arthritides.mp. or Osteoarthritis/ (44718)
- #8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (45350)
- #9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (44727
- #10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (59473)
- #11 Harpagophytum.mp. or exp Harpagophytum/(149)
- #12 Harpagophytums.mp. or exp Harpagophytum/ (83)
- #13 Harpagophytum procumbens.mp. or exp Harpagophytum/ (135)
- #14 Harpagophytum procumben.mp. or exp Harpagophytum/ (82)
- #15 procumben, Harpagophytum.mp. or exp Harpagophytum/ (82)
- #16 procumbens, Harpagophytum.mp. or exp Harpagophytum/ (82)
- #17 Devils Claw.mp. or exp Harpagophytum/ (116)
- #18 Claw, Devils.mp. or exp Harpagophytum/ (83)
- #19 Claws, Devils.mp. or exp Harpagophytum/ (82)
- #20 Devils Claws.mp. or exp Harpagophytum/ (82)
- #21 Exp Harpagophytum/ (82)
- #22 Exp Harpagophytum/ (82)
- #23 Harpagophytum/ (82)
- #24 11or12or13or14or15or16or17or18or19or20or21or22or23 (164)
- **#25 10 and 24 (37)**

APÊNDICE B. Descritores de plantas para a utilização na estratégia de busca

PLANTAS	TERMOS DO MESH	OUTROS TERMOS
***Harpagophytum procumbens DC.* ex Meisn.**	"**Harpagophytum"**	Harpagophytums OR Harpagophytum procumbens OR Harpagophytum procumben OR procumben, Harpagophytum OR procumbens, Harpagophytum OR Devils Claw OR Claw, Devils OR Claws, Devils OR Devils Claws OR Uncaria procumbens OR Uncaria procumben OR procumben, Uncaria OR procumbens, Uncaria
Uncaria tomentosa (Willd.) DC.; Uncaria guianensis (Aubl.) J.F. Gmel.	**"Uncaria" OR 'Cat's Claw"**	Cat Claw OR Cat's Claws OR Cats Claw OR Claw, Cat's OR Claws, Cat's OR Uncaria tomentosa OR Uncaria tomentosas OR tomentosa, Uncaria OR tomentosas, Uncaria
Alpinia speciosa K. Schum.; Alpinia zerumbet (Pers.) B.L. Burtt & R.M. Sm.	**"Alpinia"**	Alpinias OR Alpinia galanga OR Alpinia galangas OR galanga, Alpinia OR galangas, Alpinia OR Galanga OR Galangas
Boswellia serrata Roxb. ex Colebr.	**"Boswellia"**	Boswellia sacra OR Boswellia serrata OR Boswellia carteri OR Boswellia carterii
Bowdichia virgilioides Kunt.	**"Bowdichia"**	7,8,4'-trimethoxyisoflavone OR 7,8,4'-trimethoxyisoflavanone OR bowdichine OR bowdenol
Curcuma longa L.	**"Curcuma"**	Curcuma OR Curcumas OR Tumeric OR Tumerics OR Turmeric OR Turmerics OR Curcuma zedoaria OR Curcuma zedoarias OR zedoaria, Curcuma OR zedoarias, Curcuma OR Zedoary zedoaria OR Zedoary zedoarias OR zedoaria, Zedoary OR zedoarias, Zedoary OR Curcuma longa OR Curcuma longas OR longa, Curcuma OR longas, Curcuma
Chenopodium ambrosioides L.	**"Chenopodium"**	Chenopodium ambrosioide OR ambrosioide, Chenopodium OR ambrosioides, Chenopodium OR Wormseed OR Wormseeds OR Epazote OR Epazotes
Cordia curassavica (Jacq.) Roem. & Schult., Cordia verbenacea DC.	**"Cordia"**	Cordia OR Cordias OR Manjack OR Manjacks
Salix alba L., Salix daphnoides Vill, Salix purpurea L.	**"Salix"**	Salices OR Willow OR Willows OR Cortex Salicis OR Cortex Salici OR Salici, Cortex OR Salicis, Cortex
Persea gratissima Gaertn.f. (or Persea americana Mill.)	**"Persea"**	Perseas OR Persea americana OR Persea americanas OR americana, Persea OR americanas, Persea OR Avocado OR Avocados
Zingiber officinale Roscoe	**"Ginger"**	Gingers OR Zingiber officinale OR Zingiber officinales OR officinale, Zingiber OR officinales, Zingiber

Fonte: Elaboração Própria

APÊNDICE C – Estratégia de Busca para as diferentes bases de dados

The Cochrane Central Register of Controlled Trials (CENTRAL)

#Boswellia (54)
#Bowdichia (0)
#Chenopodium (6)
#Cordia (2)
Curcuma (108)
#Harpagophytum (18)
#Persea (2)
#Salix (13)
#Uncaria (23)
Ginger (11)

MEDLINE

Harpagophytum procumbens DC. ex Meisn.
#1 exp Osteoarthritis/ or Osteoarthrits.mp. (57958)
#2 Osteoarthritides.mp. or exp Osteoarthritis/ (44712)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/ (45663)
#4 Osteoarthroses.mp. or exp Osteoarthritis/ (44719)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/ (44737)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/ (44711)
#7 Degenerative Arthritides.mp. or Osteoarthritis/ (44718)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (45350)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (44727
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (59473)
#11 Harpagophytum.mp. or exp Harpagophytum/(149)
#12 Harpagophytums.mp. or exp Harpagophytum/ (83)
#13 Harpagophytum procumbens.mp. or exp Harpagophytum/ (135)
#14 Harpagophytum procumben.mp. or exp Harpagophytum/ (82)
#15 procumben, Harpagophytum.mp. or exp Harpagophytum/ (82)
#16 procumbens, Harpagophytum.mp. or exp Harpagophytum/ (82)
#17 Devils Claw.mp. or exp Harpagophytum/ (116)
#18 Claw, Devils.mp. or exp Harpagophytum/ (83)
#19 Claws, Devils.mp. or exp Harpagophytum/ (82)
#20 Devils Claws.mp. or exp Harpagophytum/ (82)
#21 Uncaria procumbens.mp. or exp Harpagophytum/ (82)
#22 Uncaria procumben.mp. or exp Harpagophytum/ (82)
#23 procumbens, Uncaria.mp. or Harpagophytum/ (82)
#24 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (164)
#25 10 and 24 (38)

Salix alba L., *Salix daphnoides* Vill, *Salix purpurea* L.
#1 exp Osteoarthritis/ or Osteoarthrits.mp. (57958)
#2 Osteoarthritides.mp. or exp Osteoarthritis/ (44712)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/ (45663)
#4 Osteoarthroses.mp. or exp Osteoarthritis/ (44719)

#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/ (44737)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/ (44711)
#7 Degenerative Arthritides.mp. or Osteoarthritis/ (44718)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (45350)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (44727
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (59473)
#11 Salix.mp. or exp Salix/ (1021)
#12 Salices.mp. or exp Salix/ (606)
#13 Willow.mp. or exp Salix/ (1235)
#14 Willows.mp. or exp Salix/ (682)
#15 Cortex Salicis.mp. or exp Salix/ (606)
#16 Cortex Salici.mp. or exp Salix/ (605)
#17 Salici, Cortex.mp. or exp Salix/ (605)
#18 Salicis, Cortex.mp. or exp Salix/ (606)
#19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (1517)
#20 10 and 19 (19)

Uncaria tomentosa (Willd.) DC. e *Uncaria guianensis* (Aubl.) J.F. Gmel.
#1 exp Osteoarthritis/ or Osteoarthrits.mp. (57958)
#2 Osteoarthritides.mp. or exp Osteoarthritis/ (44712)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/ (45663)
#4 Osteoarthroses.mp. or exp Osteoarthritis/ (44719)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/ (44737)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/ (44711)
#7 Degenerative Arthritides.mp. or Osteoarthritis/ (44718)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (45350)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (44727
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (59473)
#11 uncaria.mp. or exp Uncaria/ (401)
#12 Cat Claw.mp. or exp Cat's Claw/ (94)
#13 Cat's Claws.mp. or exp Cat's Claw/ (92)
#14 Cats Claw.mp. or exp Cat's Claw/ (131)
#15 Claw, Cat's.mp. or exp Cat's Claw/ (91)
#16 Claws, Cat's.mp. or exp Cat's Claw/ (91)
#17 Uncaria tomentosa.mp. or exp Cat's Claw/ (141)
#18 Uncaria tomentosas.mp. or exp Cat's Claw/ (91)
#19 tomentosa, Uncaria.mp. or exp Cat's Claw/ (91)
#20 tomentosas, Uncaria.mp. or exp Cat's Claw/ (91)
#21 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (425)
#22 10 and 21 (6)

Curcuma longa L. (ou *Curcuma domestica* Valeton)
#1 exp Osteoarthritis/ or Osteoarthrits.mp. (57958)
#2 Osteoarthritides.mp. or exp Osteoarthritis/ (44712)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/ (45663)
#4 Osteoarthroses.mp. or exp Osteoarthritis/ (44719)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/ (44737)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/ (44711)

#7 Degenerative Arthritides.mp. or Osteoarthritis/ (44718)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (45350)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (44727
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (59473)
#11 curcuma.mp. or exp Curcuma/ (2221)
#12 Curcumas.mp. or exp Curcuma/ (1062)
#13 Tumeric.mp. or exp Curcuma/ (1112)
#14 Tumerics.mp. or exp Curcuma/ (1061)
#15 Turmeric.mp. or exp Curcuma/ (2280)
#16 Turmerics.mp. or exp Curcuma/ (1062)
#17 Curcuma zedoaria.mp. or exp Curcuma/ (1104)
#18 Curcuma zedoarias.mp. or exp Curcuma/ (1061)
#19 zedoaria, Curcuma.mp. or exp Curcuma/ (1061)
#20 zedoarias, Curcuma.mp. or exp Curcuma/ (1061)
#21 Zedoary zedoaria.mp. or exp Curcuma/ (1061)
#22 Zedoary zedoarias.mp. or exp Curcuma/ (1061)
#23 zedoaria, Zedoary.mp. or exp Curcuma/ (1062)
#24 zedoarias, Zedoary.mp. or exp Curcuma/ (1061)
#25 Curcuma longa.mp. or exp Curcuma/ (1925)
#26 Curcuma longas.mp. or exp Curcuma/ (1061)
#27 longa, Curcuma.mp. or exp Curcuma/ (1065)
#28 longas, Curcuma.mp. or exp Curcuma/ (1061)
#29 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (3122)
#30 10 and 29 (24)

Cordia curassavica (Jacq.) Roem. & Schult. (ou *Cordia verbenacea* DC.)
#1 exp Osteoarthritis/ or Osteoarthrits.mp. (57958)
#2 Osteoarthritides.mp. or exp Osteoarthritis/ (44712)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/ (45663)
#4 Osteoarthroses.mp. or exp Osteoarthritis/ (44719)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/ (44737)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/ (44711)
#7 Degenerative Arthritides.mp. or Osteoarthritis/ (44718)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (45350)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (44727
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (59473)
#11 cordia.mp. or exp Cordia/ (180)
#12 cordias.mp. or exp Cordia/ (80)
#13 Manjack.mp. or exp Cordia/ (80)
#14 Manjacks.mp. or exp Cordia/ (80)
#15 11 or 12 or 13 or 14 (180)
#16 10 and 15 (0)

Zingiber officinale Roscoe.
#1 exp Osteoarthritis/ or Osteoarthrits.mp. (57958)
#2 Osteoarthritides.mp. or exp Osteoarthritis/ (44712)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/ (45663)

#4 Osteoarthroses.mp. or exp Osteoarthritis/ (44719)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/ (44737)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/ (44711)
#7 Degenerative Arthritides.mp. or Osteoarthritis/ (44718)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (45350)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (44727
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (59473)
#11 Ginger.mp. or exp Ginger/ (1836)
#12 Gingers.mp. or exp Ginger/ (900)
#13 Zingiber officinale.mp. or exp Ginger/ (1197)
#14 Zingiber officinales.mp. or exp Ginger/ (879)
#15 officinale, Zingiber.mp. or exp Ginger/ (878)
#16 officinales, Zingiber.mp. or exp Ginger/ (878)
#17 11 or 12 or 13 or 14 or 15 or 16 (1993)
#18 10 and 17 (43)

Chenopodium ambrosioides L.
#1 exp Osteoarthritis/ or Osteoarthrits.mp. (57958)
#2 Osteoarthritides.mp. or exp Osteoarthritis/ (44712)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/ (45663)
#4 Osteoarthroses.mp. or exp Osteoarthritis/ (44719)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/ (44737)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/ (44711)
#7 Degenerative Arthritides.mp. or Osteoarthritis/ (44718)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (45350)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (44727
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (59473)
#11 Chenopodium ambrosioides.mp. or exp Chenopodium ambrosioides/ (89)
#12 Chenopodium ambrosioide.mp. or exp Chenopodium ambrosioides/ (41)
#13 ambrosioide, Chenopodium.mp. or exp Chenopodium ambrosioides/ (40)
#14 ambrosioides, Chenopodium.mp. or exp Chenopodium ambrosioides/ (40)
#15 Wormseed.mp. or exp Chenopodium ambrosioides/ (50)
#16 Wormseeds.mp. or exp Chenopodium ambrosioides/ (40)
#17 Epazote.mp. or exp Chenopodium ambrosioides/ (45)
#18 Epazotes.mp. or exp Chenopodium ambrosioides/ (40)
#19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (98)
#20 10 and 19 (0)

Persea gratissima Gaertn.f
#1 exp Osteoarthritis/ or Osteoarthrits.mp. (57958)
#2 Osteoarthritides.mp. or exp Osteoarthritis/ (44712)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/ (45663)
#4 Osteoarthroses.mp. or exp Osteoarthritis/ (44719)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/ (44737)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/ (44711)
#7 Degenerative Arthritides.mp. or Osteoarthritis/ (44718)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (45350)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (44727

#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (59473)
#11 persea.mp. or exp Persea/(489)
#12 Peseas.mp. or exp Persea/ (306)
#13 Persea americana.mp. or exp Persea/ (456)
#14 Persea americanas.mp. or exp Persea/ (306)
#15 americana, Persea.mp. or exp Persea/ (306)
#16 americanas, Persea.mp. or exp Persea/ (306)
#17 Avocado.mp. or exp Persea/ (907)
#18 Avocado.mp. or exp Persea/ (907)
#19 Avocados.mp. or exp Persea/ (355)
#20 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (1002)
#21 10 and 20 (57)

Bowdichia virgilioides Kunth
#1 exp Osteoarthritis/ or Osteoarthrits.mp. (57958)
#2 Osteoarthritides.mp. or exp Osteoarthritis/ (44712)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/ (45663)
#4 Osteoarthroses.mp. or exp Osteoarthritis/ (44719)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/ (44737)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/ (44711)
#7 Degenerative Arthritides.mp. or Osteoarthritis/ (44718)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (45350)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (44727
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (59473)
#11 Bowdichia.mp. (16)
#12 7,8,4'-trimethoxyisoflavone.mp. (1)
#13 7,8,4'-trimethoxyisoflavanone.mp. (1)
#14 bowdichine.mp. (1)
#15 bowdenol.mp. (2)
#16 11 or 12 or 13 or 14 or 15 (16)
#17 11 or 12 or 13 or 14 or 15 (16)
#18 10 and 16 (0)

Boswellia serrata Roxb. ex Colebr.
#1 exp Osteoarthritis/ or Osteoarthrits.mp. (57958)
#2 Osteoarthritides.mp. or exp Osteoarthritis/ (44712)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/ (45663)
#4 Osteoarthroses.mp. or exp Osteoarthritis/ (44719)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/ (44737)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/ (44711)
#7 Degenerative Arthritides.mp. or Osteoarthritis/ (44718)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (45350)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (44727
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (59473)
(23)

EMBASE

Harpagophytum procumbens DC. ex Meisn.
#1 Osteoarthritis.mp. or exp osteoarthritis/(93973)
#2 Osteoarthritides.mp. (2)
#3 Osteoarthrosis.mp. or exp osteoarthritis/(84625)
#4 Osteoarthroses.mp. or exp osteoarthritis/(83910)
#5 Arthritis, Degenerative.mp. or exp osteoarthritis/(83932)
#6 exp osteoarthritis/ or Arthritides, Degenerative.mp. (83904)
#7 exp osteoarthritis/ or Degenerative Arthritides.mp. (83911)
#8 Degenerative Arthritis.mp. or exp osteoarthritis/(84367)
#9 exp osteoarthritis/ or Osteoarthrosis Deformans.mp. (83923)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (95116)
#11 exp Harpagophytum extract/ or Harpagophytum.mp. or exp Harpagophytum/ or exp Harpagophytum procumbens extract/ (423)
#12 exp Harpagophytum extract/ or Harpagophytums.mp. or exp Harpagophytum/ or exp Harpagophytum procumbens extract/ (371)
#13 Harpagophytum procumbens.mp. or exp Harpagophytum/ (361)
#14 exp Harpagophytum procumbens extract/ or exp Harpagophytum/ or procumbens, Harpagophytum.mp. or exp Harpagophytum extract/ or exp harpagophytum procumbens/ (371)
#15 Devils Claw.mp. or exp Harpagophytum/ (273)
#16 exp Harpagophytum extract/ or exp Harpagophytum/ or exp Harpagophytum procumbens extract/ or Claw, Devils.mp. (371)
#17 Devils Claws.mp. or exp Harpagophytum/ (186)
#18 procumbens, Uncaria.mp. or exp Harpagophytum extract/ or exp Harpagophytum procumbens extract/ (274)
#19 Uncaria procumben.mp. or exp Harpagophytum extract/ or exp Harpagophytum procumbens extract/ (274)
#20 Uncaria procumbens.mp. or exp Harpagophytum extract/ or exp Harpagophytum procumbens extract/ (274
#21 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (446)
#22 10 and 21 (120)

Salix alba L., *Salix daphnoides* Vill, *Salix purpurea* L.
#1 Osteoarthritis.mp. or exp osteoarthritis/(93973)
#2 Osteoarthritides.mp. (2)
#3 Osteoarthrosis.mp. or exp osteoarthritis/(84625)
#4 Osteoarthroses.mp. or exp osteoarthritis/(83910)
#5 Arthritis, Degenerative.mp. or exp osteoarthritis/(83932)
#6 exp osteoarthritis/ or Arthritides, Degenerative.mp. (83904)
#7 exp osteoarthritis/ or Degenerative Arthritides.mp. (83911)
#8 Degenerative Arthritis.mp. or exp osteoarthritis/(84367)
#9 exp osteoarthritis/ or Osteoarthrosis Deformans.mp. (83923)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (95116)
#11 Salix.mp. or exp willow/ (1811)
#12 Salices.mp. or exp willow/(1064)
#13 exp willow/ or Willow.mp. (1698)
#14 exp willow/ or Willows.mp. (1147)
#15 exp Salix extract/ or exp willow/ or Cortex Salicis.mp. (1152)

#16 exp Salix extract/ or exp willow/ or Cortex Salici.mp. (1151)
#17 exp Salix extract/ or Salicis, Cortex.mp. or exp willow/ (1158)
#18 11 or 12 or 13 or 14 or 15 or 16 or 17 (2328)
#19 10 and 18 (85)

Uncaria tomentosa (Willd.) DC. e *Uncaria guianensis* (Aubl.) J.F. Gmel.
#1 Osteoarthritis.mp. or exp osteoarthritis/(93973)
#2 Osteoarthritides.mp. (2)
#3 Osteoarthrosis.mp. or exp osteoarthritis/(84625)
#4 Osteoarthroses.mp. or exp osteoarthritis/(83910)
#5 Arthritis, Degenerative.mp. or exp osteoarthritis/(83932)
#6 exp osteoarthritis/ or Arthritides, Degenerative.mp. (83904)
#7 exp osteoarthritis/ or Degenerative Arthritides.mp. (83911)
#8 Degenerative Arthritis.mp. or exp osteoarthritis/(84367)
#9 exp osteoarthritis/ or Osteoarthrosis Deformans.mp. (83923)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (95116)
#11 exp Uncaria tomentosa/ or uncaria.mp. or exp Uncaria/ or exp Uncaria tomentosa extract/ (744)
#12 exp Uncaria tomentosa/ or exp Uncaria tomentosa extract/ or Cat Claw.mp. (289)
#13 Cat's Claws.mp. or exp Uncaria tomentosa/ (193)
#14 Cats Claw.mp. or exp Uncaria tomentosa/ (245)
#15 exp Uncaria tomentosa/ or exp Uncaria tomentosa extract/ or Claw, Cat's.mp. (292)
#16 exp Uncaria tomentosa extract/ or Claws, Cat's.mp. (210)
#17 exp Uncaria tomentosa extract/ or Uncaria (326)
#18 Uncaria tomentosas.mp. or exp Uncaria tomentosa/ (191)
#19 exp Uncaria tomentosa/ or exp Uncaria tomentosa extract/ or tomentosa, Uncaria.mp. (292)
#20 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (853)
#21 10 and 20 (41)

Curcuma longa L. (ou *Curcuma domestica* Valeton)
#1 Osteoarthritis.mp. or exp osteoarthritis/(93973)
#2 Osteoarthritides.mp. (2)
#3 Osteoarthrosis.mp. or exp osteoarthritis/(84625)
#4 Osteoarthroses.mp. or exp osteoarthritis/(83910)
#5 Arthritis, Degenerative.mp. or exp osteoarthritis/(83932)
#6 exp osteoarthritis/ or Arthritides, Degenerative.mp. (83904)
#7 exp osteoarthritis/ or Degenerative Arthritides.mp. (83911)
#8 Degenerative Arthritis.mp. or exp osteoarthritis/(84367)
#9 exp osteoarthritis/ or Osteoarthrosis Deformans.mp. (83923)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (95116)
#11 exp Curcuma longa extract/ or exp Curcuma zedoaria/ or exp Curcuma/ or Curcuma.mp. or exp Curcuma zedoaria extract/ or exp Curcuma longa (4007)
#12 exp Curcuma longa extract/ or exp Curcuma zedoaria/ or exp Curcuma/ or curcumas.mp. or exp Curcuma zedoaria extract/ or exp Curcuma longa/ (2921)
#13 exp Curcuma longa/ or Tumeric.mp. (1970)

#14 Turmerics.mp. or exp Curcuma longa/ or exp turmeric/ or exp Curcuma longa extract/ (3133)
#15 exp Curcuma longa/ or tumerics.mp. (1898)
#16 turmeric.mp. or exp Curcuma longa/ or exp turmeric/ or exp Curcuma longa extract/ (4184)
#17 exp Curcuma zedoaria extract/ or exp Curcuma (201)
#18 exp Curcuma zedoaria extract/ or exp Curcuma zedoaria/ or Curcuma zedoarias.mp. (157)
#19 zedoaria, Curcuma.mp. or exp Curcuma zedoaria extract/ or exp Curcuma zedoaria/ (157)
#20 exp Curcuma zedoaria extract/ or Zedoary zedoaria.mp. (119)
#21 exp Curcuma zedoaria extract/ or Zedoary zedoarias.mp. (119)
#22 exp Curcuma zedoaria extract/ or zedoaria, Zedoary.mp. (120)
#23 Curcuma longa.mp. or exp Curcuma longa/ (3159)
#24 Curcuma longas.mp. or exp Curcuma longa/ (1898)
#25 exp Curcuma longa/ or longa, Curcuma.mp. or exp Curcuma longa extract/ (6433)
#26 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (5417)
#27 10 and 26 (119)

Cordia curassavica (Jacq.) Roem. & Schult. (ou *Cordia verbenacea* DC.)
#1 Osteoarthritis.mp. or exp osteoarthritis/(93973)
#2 Osteoarthritides.mp. (2)
#3 Osteoarthrosis.mp. or exp osteoarthritis/(84625)
#4 Osteoarthroses.mp. or exp osteoarthritis/(83910)
#5 Arthritis, Degenerative.mp. or exp osteoarthritis/(83932)
#6 exp osteoarthritis/ or Arthritides, Degenerative.mp. (83904)
#7 exp osteoarthritis/ or Degenerative Arthritides.mp. (83911)
#8 Degenerative Arthritis.mp. or exp osteoarthritis/(84367)
#9 exp osteoarthritis/ or Osteoarthrosis Deformans.mp. (83923)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (95116)
#11 exp Cordia/ or cordia.mp. (358)
#12 cordias.mp. (0)
#13 11 or 12 (358)
#14 10 and 13 (0)

Chenopodium ambrosioides L.
#1 exp Osteoarthritis/ or Osteoarthrits.mp. (57958)
#2 Osteoarthritides.mp. or exp Osteoarthritis/ (44712)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/ (45663)
#4 Osteoarthroses.mp. or exp Osteoarthritis/ (44719)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/ (44737)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/ (44711)
#7 Degenerative Arthritides.mp. or Osteoarthritis/ (44718)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (45350)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (44727
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (59473)

#11 Chenopodium ambrosioides.mp. or exp Chenopodium ambrosioides/ (89)
#12 Chenopodium ambrosioide.mp. or exp Chenopodium ambrosioides/ (41)
#13 ambrosioide, Chenopodium.mp. or exp Chenopodium ambrosioides/ (40)
#14 ambrosioides, Chenopodium.mp. or exp Chenopodium ambrosioides/ (40)
#15 Wormseed.mp. or exp Chenopodium ambrosioides/ (50)
#16 Wormseeds.mp. or exp Chenopodium ambrosioides/ (40)
#17 Epazote.mp. or exp Chenopodium ambrosioides/ (45)
#18 Epazotes.mp. or exp Chenopodium ambrosioides/ (40)
#19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (98)
#20 10 and 19 (0)

Boswellia serrata Roxb. ex Colebr #1 Osteoarthritis.mp. or exp osteoarthritis/(93973)
#2 Osteoarthritides.mp. (2)
#3 Osteoarthrosis.mp. or exp osteoarthritis/(84625)
#4 Osteoarthroses.mp. or exp osteoarthritis/(83910)
#5 Arthritis, Degenerative.mp. or exp osteoarthritis/(83932)
#6 exp osteoarthritis/ or Arthritides, Degenerative.mp. (83904)
#7 exp osteoarthritis/ or Degenerative Arthritides.mp. (83911)
#8 Degenerative Arthritis.mp. or exp osteoarthritis/(84367)
#9 exp osteoarthritis/ or Osteoarthrosis Deformans.mp. (83923)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (95116)
#11 exp Boswellia serrata extract/ or exp Boswellia/ or exp Boswellia serrata/ or exp Boswellia sacra/ or Boswellia.mp. (812)
#12 Boswellia sacra.mp. or exp Boswellia sacra/ (46)
#13 exp Boswellia serrata extract/ or Boswellia serrata.mp. or exp Boswellia serrata/ (487)
#14 Boswellia carteri.mp. or exp Boswellia sacra/ (62)
#15 Boswellia carterii.mp. or exp Boswellia sacra/ (102)
#16 11 or 12 or 13 or 14 or 15 (931)
#17 10 and 16 (100)

Zingiber officinale Roscoe.
#1 Osteoarthritis.mp. or exp osteoarthritis/(93973)
#2 Osteoarthritides.mp. (2)
#3 Osteoarthrosis.mp. or exp osteoarthritis/(84625)
#4 Osteoarthroses.mp. or exp osteoarthritis/(83910)
#5 Arthritis, Degenerative.mp. or exp osteoarthritis/(83932)
#6 exp osteoarthritis/ or Arthritides, Degenerative.mp. (83904)
#7 exp osteoarthritis/ or Degenerative Arthritides.mp. (83911)
#8 Degenerative Arthritis.mp. or exp osteoarthritis/(84367)
#9 exp osteoarthritis/ or Osteoarthrosis Deformans.mp. (83923)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (95116)
#11 exp ginger extract/ or exp ginger/ or ginger.mp. (4632)
#12 exp ginger extract/ or exp ginger/ or Gingers.mp. (4036)
#13 Zingiber officinale.mp. or exp ginger/ (3202)
#14 Zingiber officinales.mp. or exp ginger/ (2864)
#15 ginger/ or exp ginger extract/ or officinale, Zingiber.mp. (4023)
#16 exp ginger/ or exp ginger extract/ or officinales, Zingiber.mp. (4023)

#17 11 or 12 or 13 or 14 or 15 or 16 (5332)
#18 10 and 17 (197)

Persea gratissima Gaertn.f
#1 Osteoarthritis.mp. or exp osteoarthritis/(93973)
#2 Osteoarthritides.mp. (2)
#3 Osteoarthrosis.mp. or exp osteoarthritis/(84625)
#4 Osteoarthroses.mp. or exp osteoarthritis/(83910)
#5 Arthritis, Degenerative.mp. or exp osteoarthritis/(83932)
#6 exp osteoarthritis/ or Arthritides, Degenerative.mp. (83904)
#7 exp osteoarthritis/ or Degenerative Arthritides.mp. (83911)
#8 Degenerative Arthritis.mp. or exp osteoarthritis/(84367)
#9 exp osteoarthritis/ or Osteoarthrosis Deformans.mp. (83923)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (95116)
#11 exp Persea/ or persea.mp. (897)
#12 Persea americana.mp. or exp avocado/ (805)
#13 exp Persea/ or perseas.mp. (682)
#14 Persea americanas.mp. or exp avocado/ (682)
#15 americana, Persea.mp. (0)
#16 avocado.mp. or exp avocado/ (1268)
#17 avocados.mp. or exp avocado/ (738)
#18 11 or 12 or 13 or 14 or 15 or 16 or 17 (1516)
#19 10 and 18 (116)

Bowdichia virgilioides Kunth
#1 Osteoarthritis.mp. or exp osteoarthritis/(93973)
#2 Osteoarthritides.mp. (2)
#3 Osteoarthrosis.mp. or exp osteoarthritis/(84625)
#4 Osteoarthroses.mp. or exp osteoarthritis/(83910)
#5 Arthritis, Degenerative.mp. or exp osteoarthritis/(83932)
#6 exp osteoarthritis/ or Arthritides, Degenerative.mp. (83904)
#7 exp osteoarthritis/ or Degenerative Arthritides.mp. (83911)
#8 Degenerative Arthritis.mp. or exp osteoarthritis/(84367)
#9 exp osteoarthritis/ or Osteoarthrosis Deformans.mp. (83923)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (95116)
#11 Bowdichia.mp. (42)
#12 7,8,4'-trimethoxyisoflavone.mp. (3)
#13 7,8,4'-trimethoxyisoflavanone.mp. (1)
#14 bowdichine.mp. (1)
#15 bowdenol.mp. (2)
#16 11 or 12 or 13 or 14 or 15 (44)
#17 10 and 16 (0)

CINAHL

Harpagophytum procumbens DC. ex Meisn.
#1 (MH "Osteoarthritis+") OR "" (12,445)
#2 "Osteoarthritides" (0)

#3 "Osteoarthrosis OR “Osteoarthritis " (10,749)
#4 "Osteoarthroses" (1)
#5 "Arthritis, Degenerative" (2)
#6 "Arthritides, Degenerative" (0)
#7 "Degenerative Arthritides" (2)
#8 "Degenerative Arthritis" (134)
#9 "Osteoarthrosis Deformans" (0)
#10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 (12,603)
#11 (MH "Devil's Claw") OR "Harpagophytum"
#12 "Harpagophytums" OR (MH "Devil's Claw")
#13 (MH "Devil's Claw") OR "Harpagophytum procumbens"
#14 (MH "Devil's Claw") OR "Harpagophytum procumben"
#15 (MH "Devil's Claw") OR "procumben, Harpagophytum"
#16(MH "Devil's Claw") OR "procumbens, Harpagophytum"
#17(MH "Devil's Claw") OR "Devils Claw"
#18(MH "Devil's Claw") OR "Claw, Devils"
#19 (MH "Devil's Claw") OR "Claws, Devils"
#20 (MH "Devil's Claw") OR "Claws, Devils"
#21 (MH "Devil's Claw") OR "Devils Claws"
#22 (MH "Devil's Claw") OR "Uncaria procumbens"
#23 (MH "Devil's Claw") OR "Uncaria procumben"
#24 (MH "Devil's Claw") OR "procumben, Uncaria"
#25 (MH "Devil's Claw") OR "procumbens, Uncaria"
#26 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 (
#27 S10 AND S26 (31)

Salix alba L., *Salix daphnoides* Vill, *Salix purpurea* L.
#1 (MH "Osteoarthritis+") OR "" (12,445)
#2 "Osteoarthritides" (0)
#3 "Osteoarthrosis OR “Osteoarthritis " (10,749)
#4 "Osteoarthroses" (1)
#5 "Arthritis, Degenerative" (2)
#6 "Arthritides, Degenerative" (0)
#7 "Degenerative Arthritides" (2)
#8 "Degenerative Arthritis" (134)
#9 "Osteoarthrosis Deformans" (0)
#10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 (12,603)
#11 (MH "Willow Bark") OR "salix" (49)
#12 "Salices" (0)
#13 (MH "Willow Bark") OR "Willow" (90)
#14 (MH "Willow Bark") OR "Willows" (36)
#15 "Cortex Salicis" (0)
#16 "Cortex Salicis" (0)
#17 "Cortex Salici" (0)
#18 "Salici, Cortex" (0)
#19 "Salicis, Cortex" (2)
#20 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 (103)

#21 S10 AND S20 (16)

Uncaria tomentosa (Willd.) DC. e *Uncaria guianensis* (Aubl.) J.F. Gmel.
#1 (MH "Osteoarthritis+") OR "" (12,445)
#2 "Osteoarthritides" (0)
#3 "Osteoarthrosis OR “Osteoarthritis " (10,749)
#4 "Osteoarthroses" (1)
#5 "Arthritis, Degenerative" (2)
#6 "Arthritides, Degenerative" (0)
#7 "Degenerative Arthritides" (2)
#8 "Degenerative Arthritis" (134)
#9 "Osteoarthrosis Deformans" (0)
#10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 (12,603)
#11 (MH "Cat's Claw") OR "uncaria"
#12 (MH "Cat's Claw") OR "Cat Claw"
#13 (MH "Cat's Claw") OR "Cat's Claws"
#14 (MH "Cat's Claw") OR "Cats Claw"
#15 (MH "Cat's Claw") OR "Claw, Cat's"
#16 (MH "Cat's Claw") OR "Claws, Cat's"
#17 (MH "Cat's Claw") OR "Uncaria tomentosa"
#18 (MH "Cat's Claw") OR "Uncaria tomentosas"
#19 (MH "Cat's Claw") OR "tomentosa, Uncaria"
#20 (MH "Cat's Claw") OR "tomentosas, Uncaria"
#21 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20
#22 S10 AND S21 (5)

Curcuma longa L. (ou *Curcuma domestica* Valeton)
#1 (MH "Osteoarthritis+") OR "" (12,445)
#2 "Osteoarthritides" (0)
#3 "Osteoarthrosis OR “Osteoarthritis " (10,749)
#4 "Osteoarthroses" (1)
#5 "Arthritis, Degenerative" (2)
#6 "Arthritides, Degenerative" (0)
#7 "Degenerative Arthritides" (2)
#8 "Degenerative Arthritis" (134)
#9 "Osteoarthrosis Deformans" (0)
#10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 (12,603)
#11"curcuma"(115)
#12"curcumas"(0)
#13 "tumeric"(7)
#14 "tumerics”(0)
#15 (MH "Turmeric") OR "turmeric" (183)
#16(MH "Turmeric") OR "turmerics" (50)
#17 Curcuma zedoaria" (3)
#18"Curcuma zedoaries" (0)
#19 "Zedoary zedoaria"(0)
#20 "Curcuma longa" (83)

#21"Curcuma longas" (0)
#22 "longa, Curcuma" (2)
#23 "longas, Curcuma"(0)
#24 "zedoarias, Zedoary"(0)
#25 "zedoaria, Zedoary" (1)
#26 "Zedoary zedoarias"(0)
#27 "zedoarias, Curcuma" (0)
#28 "zedoaria, Curcuma" (0)
#29 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 (315)
#30 S10 AND S29 (13)

Cordia curassavica (Jacq.) Roem. & Schult. (ou *Cordia verbenacea* DC.)
#1 (MH "Osteoarthritis+") OR "" (12,445)
#2 "Osteoarthritides" (0)
#3 "Osteoarthrosis OR “Osteoarthritis " (10,749)
#4 "Osteoarthroses" (1)
#5 "Arthritis, Degenerative" (2)
#6 "Arthritides, Degenerative" (0)
#7 "Degenerative Arthritides" (2)
#8 "Degenerative Arthritis" (134)
#9 "Osteoarthrosis Deformans" (0)
#10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 (12,603)
#11 "cordia" (6)
#12 "cordias" (0)
#13 "Manjack" (0)
#14"Manjacks" (0)
#15 S11 OR S12 OR S13 OR S14 (6)
#16 S10 AND S15 (0)

Boswellia serrata Roxb. ex Colebr
#1 (MH "Osteoarthritis+") OR "Osteoarthritis" (12,221)
#2 "Osteoarthritides" (0)
#3 "Osteoarthrosis" (209)
#4 "Osteoarthroses" (1)
#5 "Arthritis, Degenerative" (2)
#6 "Arthritides, Degenerative" (0)
#7 "Degenerative Arthritides" (2)
#8 "Degenerative Arthritis" (133)
#9 "Osteoarthrosis Deformans" OR (MH "Osteoarthritis+") (10,475)
#10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 (12,380)
#11 "boswellia" (0)
#12 Boswellia sacra" (0)
#13 Boswellia serrata" (31)
#14 Boswellia carteri (2)
#15 Boswellia carterii (1)
#16 S11 OR S12 OR S13 OR S14 OR S15 (52)
#17 S10 AND S16 (15)

Zingiber officinale Roscoe.
#1 (MH "Osteoarthritis+") OR " Osteoarthritis " (12,445)
#2 "Osteoarthritides" (0)
#3 "Osteoarthrosis OR “Osteoarthritis " (10,749)
#4 "Osteoarthroses" (1)
#5 "Arthritis, Degenerative" (2)
#6 "Arthritides, Degenerative" (0)
#7 "Degenerative Arthritides" (2)
#8 "Degenerative Arthritis" (134)
#9 "Osteoarthrosis Deformans" (0)
#10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 (12,603)
#11 (MH "Ginger") OR "ginger" (599)
#12 (MH "Ginger") OR "Gingers" (456)
#13 (MH "Ginger") OR "Zingiber officinale" (482)
#14 (MH "Ginger") OR "Zingiber officinales" (455)
#15 (MH "Ginger") OR "officinales, Zingiber" (455)
#16 (MH "Ginger") OR "officinales, Zingiber" (455)
#17 S11 OR S12 OR S13 OR S14 OR S15 OR S16 (664)
#18 S10 AND S17 (44)

Chenopodium ambrosioides L.
#1 (MH "Osteoarthritis+") OR " Osteoarthritis " (12,445)
#2 "Osteoarthritides" (0)
#3 "Osteoarthrosis OR “Osteoarthritis " (10,749)
#4 "Osteoarthroses" (1)
#5 "Arthritis, Degenerative" (2)
#6 "Arthritides, Degenerative" (0)
#7 "Degenerative Arthritides" (2)
#8 "Degenerative Arthritis" (134)
#9 "Osteoarthrosis Deformans" (0)
#10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 (12,603)
11"Chenopodium ambrosioides" (3)
#12 "Chenopodium ambrosioide" (0)
#13 "ambrosioide, Chenopodium" (0)
#14 "ambrosioides, Chenopodium" (0)
#15 "Wormseed" (0)
#16 "Wormseeds" (0)
#17 "Epazote" (0)
#18 "Epazotes" (0)
#19 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 (3)
#20 S10 AND S19 (0)

Persea gratissima Gaertn.f
#1 (MH "Osteoarthritis+") OR " Osteoarthritis " (12,445)
#2 "Osteoarthritides" (0)
#3 "Osteoarthrosis OR “Osteoarthritis " (10,749)
#4 "Osteoarthroses" (1)

#5 "Arthritis, Degenerative" (2)
#6 "Arthritides, Degenerative" (0)
#7 "Degenerative Arthritides" (2)
#8 "Degenerative Arthritis" (134)
#9 "Osteoarthrosis Deformans" (0)
#10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 (12,603)
#11 (MH "Avocado") OR "persea" (108)
#12 (MH "Avocado") OR "Perseas" (106)
#13 (MH "Avocado") OR "Persea americanas" (106)
#14 (MH "Avocado") OR "americanas, Persea" (106)
#15 (MH "Avocado") OR "americana,persea" (106)
#16 (MH "Avocado") OR "Avocado" (137)
#17 (MH "Avocado") OR "persea americana" (106)
#18 (MH "Avocado") OR "avocados" (117)
#19 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 (158)
#20 S10 AND S19 (24)

Bowdichia virgilioides Kunth
#1 (MH "Osteoarthritis+") OR " Osteoarthritis " (12,445)
#2 "Osteoarthritides" (0)
#3 "Osteoarthrosis OR “Osteoarthritis " (10,749)
#4 "Osteoarthroses" (1)
#5 "Arthritis, Degenerative" (2)
#6 "Arthritides, Degenerative" (0)
#7 "Degenerative Arthritides" (2)
#8 "Degenerative Arthritis" (134)
#9 "Osteoarthrosis Deformans" (0)
#10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 (12,603)
#11 "Bowdichia" (1)
#12 "7,8,4'-trimethoxyisoflavone" (0)
#13 "7,8,4'-trimethoxyisoflavanone" (0)
#14 "bowdichine" (0)
#15 "bowdenol" (0)
#16 S11 OR S12 OR S13 OR S14 OR S15 (1)
#17 S10 AND S16 (0)

Web of Science

Harpagophytum procumbens DC. ex Meisn.
#1Tópico: (Osteoarthritis) *OR* Tópico: (Osteoarthritides) *OR* Tópico: (Osteoarthrosis) *OR* Tópico: (Osteorthroses) *OR*Tópico: (Arthritis,Degenerative) *OR* Tópico: (Arthritides, degenerative) *OR* Tópico: (Degenerative Arthritides) *OR* Tópico:(Degenerative Arthritis) *OR* Tópico: (Osteoarthrosis Deformans) (144.232)
#2Tópico: (Harpagophytum) *OR* Tópico: (Harpagophytums) *OR* Tópico: (Harpagophytum procumbens) *OR* Tópico:(Harpagophytum procumben) *OR* Tópico: (procumben, Harpagophytum) *OR* Tópico: (procumbens, Harpagophytum) *OR*Tópico: (Devils Claw) *OR* Tópico: (Claw, Devils) *OR* Tópico: (Claws, Devils) *OR* Tópico: (Devils Claws) *OR* Tópico:(Uncaria procumbens) *OR* Tópico: (Uncaria

procumben) *OR* Tópico: (procumben, Uncaria) *OR* Tópico: (procumbens, Uncaria) (469)
#3 #2 AND #1 (88)

Salix alba L., *Salix daphnoides* Vill, *Salix purpurea* L.
#1Tópico: (Osteoarthritis) *OR* Tópico: (Osteoarthritides) *OR* Tópico: (Osteoarthrosis) *OR* Tópico: (Osteo rthroses) *OR*Tópico: (Arthritis, Degenerative) *OR* Tópico: (Arthritides, Degenerative) *OR* Tópico: (Degenerative Arthritides) *OR* Tópico:(Degenerative Arthritis) *OR* Tópico: (Osteoarthrosis Deformans) (144.232)
#2Tópico: (salix) *OR* Tópico: (salices) *OR* Tópico: (Willow) *OR* Tópico: (Willows) *OR* Tópico: (Cortex Salicis) *OR* Tópico:(Cortex Salici) *OR* Tópico: (Salici, Cortex) *OR* Tópico: (Salicis, Cortex) (26.060)
#3 #1 AND #2 (52)

Uncaria tomentosa (Willd.) DC. e *Uncaria guianensis* (Aubl.) J.F. Gmel.
#1Tópico: (Osteoarthritis) *OR* Tópico: (Osteoarthritides) *OR* Tópico: (Osteoarthrosis) *OR* Tópico: (Osteo rthroses) *OR*Tópico: (Arthritis, Degenerative) *OR* Tópico: (Arthritides, Degenerative) *OR* Tópico: (Degenerative Arthritides) *OR* Tópico:(Degenerative Arthritis) *OR* Tópico: (Osteoarthrosis Deformans) (144.232)
#2Tópico: (uncaria) *OR* Tópico: (Cat Claw) *OR* Tópico: (Cat's Claws) *OR* Tópico: (Cats Claw) *OR* Tópico: (Claw, Cat's) *OR*Tópico: (Claws, Cat's) *OR* Tópico: (Uncaria tomentosa) *OR* Tópico: (Uncaria tomentosas) *OR* Tópico: (tomentosa, Uncaria) *OR* Tópico: (tomentosas, Uncaria) (1320)
#3 #1 AND #2 (19)

Curcuma longa L. (ou *Curcuma domestica* Valeton)
#1Tópico: (Osteoarthritis) *OR* Tópico: (Osteoarthritides) *OR* Tópico: (Osteoarthrosis) *OR* Tópico: (Osteo rthroses) *OR*Tópico: (Arthritis, Degenerative) *OR* Tópico: (Arthritides, Degenerative) *OR* Tópico: (Degenerative Arthritides) *OR* Tópico:(Degenerative Arthritis) *OR* Tópico: (Osteoarthrosis Deformans) (144.232)
#2Tópico: (curcuma) *OR* Tópico: (curcumas) *OR* Tópico: (Tumeric) *OR* Tópico: (Tum erics) *OR* Tópico: (Turmeric) *OR*Tópico: (Turmerics) *OR* Tópico: (Curcuma zedoaria) *OR* Tópico: (Curcuma zedoarias) *OR* Tópico: (zedoaria, Curcuma)*OR* Tópico: (zedoarias, Curcuma) *OR* Tópico: (Zedoary zedoaria) *OR* Tópico: (Zedoary zedoarias) *OR* Tópico: (zedoaria, Zedoary) *OR* Tópico: (zedoarias, Zedoary) *OR* Tópico: (Curcuma longa) *OR* Tópico: (Curcuma longas) *OR* Tópico: (longa, Curcuma) *OR* Tópico: (longas, Curcuma) (12664)
#3 #1 AND #2 (61)

Cordia curassavica (Jacq.) Roem. & Schult. (ou *Cordia verbenacea* DC.)
#1Tópico: (Osteoarthritis) *OR* Tópico: (Osteoarthritides) *OR* Tópico: (Osteoarthrosis) *OR* Tópico: (Osteo rthroses) *OR*Tópico: (Arthritis,

Degenerative) *OR* Tópico: (Arthritides, Degenerative) *OR* Tópico: (Degenerative Arthritides) *OR* Tópico:(Degenerative Arthritis) *OR* Tópico: (Osteoarthrosis Deformans) (144.232)
#2
Tópico: (cordia) *OR* Tópico: (cordias) *OR* Tópico: (Manjack) *OR* Tópico: (Manjacks) (1554)
#3 #1 AND #2 (0)

Boswellia serrata Roxb. ex Colebr
#1Tópico: (Osteoarthritis) *OR* Tópico: (Osteoarthritides) *OR* Tópico: (Osteoarthrosis) *OR* Tópico: (Osteo rthroses) *OR*Tópico: (Arthritis, Degenerative) *OR* Tópico: (Arthritides, Degenerative) *OR* Tópico: (Degenerative Arthritides) *OR* Tópico:(Degenerative Arthritis) *OR* Tópico: (Osteoarthrosis Deformans) (144.232)
#2Tópico: (Boswellia) *OR* Tópico: (Boswellia sacra) *OR* Tópico: (Boswellia serrata) *OR* Tópico: (Boswellia carteri) *OR* Tópico: (Boswellia carterii)
#3 #1 AND #2 (64)

Zingiber officinale Roscoe.
#1Tópico: (Osteoarthritis) *OR* Tópico: (Osteoarthritides) *OR* Tópico: (Osteoarthrosis) *OR* Tópico: (Osteo rthroses) *OR*Tópico: (Arthritis, Degenerative) *OR* Tópico: (Arthritides, Degenerative) *OR* Tópico: (Degenerative Arthritides) *OR* Tópico:(Degenerative Arthritis) *OR* Tópico: (Osteoarthrosis Deformans) (144.232)
(110)

Chenopodium ambrosioides L.
#1Tópico: (Osteoarthritis) *OR* Tópico: (Osteoarthritides) *OR* Tópico: (Osteoarthrosis) *OR* Tópico: (Osteo rthroses) *OR*Tópico: (Arthritis, Degenerative) *OR* Tópico: (Arthritides, Degenerative) *OR* Tópico: (Degenerative Arthritides) *OR* Tópico:(Degenerative Arthritis) *OR* Tópico: (Osteoarthrosis Deformans) (144.232)
#2Tópico: (Chenopodium ambrosioides) *OR* Tópico: (Chenopodium ambrosioide) *OR* Tópico: (ambrosioide, Chenopodium)*OR* Tópico: (ambrosioides, Chenopodium) *OR* Tópico: (Wormseed) *OR* Tópico: (Wormseeds) *OR* Tópico: (Epaz ote) *OR*Tópico: (Epazotes) (496)
#3 #2 AND #1 (0)

Persea gratissima Gaertn.f
#1Tópico: (Osteoarthritis) *OR* Tópico: (Osteoarthritides) *OR* Tópico: (Osteoarthrosis) *OR* Tópico: (Osteo rthroses) *OR*Tópico: (Arthritis, Degenerative) *OR* Tópico: (Arthritides, Degenerative) *OR* Tópico: (Degenerative Arthritides) *OR* Tópico:(Degenerative Arthritis) *OR* Tópico: (Osteoarthrosis Deformans) (144.232)
#2Tópico: (persea) *OR* Tópico: (perseas) *OR* Tópico: (Persea americana) *OR* Tópico: (persea americanas) *OR* Tópico:(Avocado) *OR* Tópico: (Avocados) (125)
#3 #2 AND #1 (134)

Bowdichia virgilioides Kunth
#1Tópico: (Osteoarthritis) *OR* Tópico: (Osteoarthritides) *OR* Tópico: (Osteoarthrosis) *OR* Tópico: (Osteo rthroses) *OR*Tópico: (Arthritis, Degenerative) *OR* Tópico: (Arthritides, Degenerative) *OR* Tópico: (Degenerative Arthritides) *OR* Tópico:(Degenerative Arthritis) *OR* Tópico: (Osteoarthrosis Deformans) (144.232)
Tópico: (Bowdichia) *OR* Tópico: (7,8,4'-trimethoxyisoflavone) *OR* Tópico: (7,8,4'-trimethoxyisoflavanone) *OR* Tópico:(persea americanas) *OR* Tópico: (bowdichine) *OR* Tópico: (bowdenol) (128)
#3 #2 AND #1 (0)

HEALTH STAR

Boswellia serrata Roxb. ex Colebr
#1 Osteoarthritis.mp. or exp Osteoarthritis/(34963)
#2 Osteoarthritides.mp. or exp Osteoarthritis/(28841)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/(29335)
#4 Osteoarthroses.mp. or exp Osteoarthritis/(28844)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/(28854)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/(28841)
#7 Degenerative Arthritides.mp. or exp Osteoarthritis/ (28843)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (29215)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (28844)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9(35795)
#11 Boswellia.mp. or exp Boswellia/ (95)
#12 Boswellia serrata.mp. or exp Boswellia/ (84)
#13 exp Boswellia/ or Boswellia sacra.mp. (54)
#14 Boswellia carteri.mp. (1)
#15 exp Boswellia/ or Boswellia carterii.mp. (54)
#16 11 or 12 or 13 or 14 or 15 (95)
#17 10 and 16 (17)

Bowdichia virgilioides Kunth
#1 Osteoarthritis.mp. or exp Osteoarthritis/(34963)
#2 Osteoarthritides.mp. or exp Osteoarthritis/(28841)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/(29335)
#4 Osteoarthroses.mp. or exp Osteoarthritis/(28844)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/(28854)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/(28841)
#7 Degenerative Arthritides.mp. or exp Osteoarthritis/ (28843)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (29215)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (28844)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9(35795)
#11 bowdichia.mp. (4)
#12 10 and 11 (0)

Curcuma longa L. (ou *Curcuma domestica* Valeton)
#1 Osteoarthritis.mp. or exp Osteoarthritis/(34963)
#2 Osteoarthritides.mp. or exp Osteoarthritis/(28841)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/(29335)
#4 Osteoarthroses.mp. or exp Osteoarthritis/(28844)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/(28854)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/(28841)
#7 Degenerative Arthritides.mp. or exp Osteoarthritis/ (28843)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (29215)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (28844)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9(35795)
#11 Curcuma.mp. or exp Curcuma/ (566)
#12 curcumas.mp. or exp Curcuma/ (320)
#13 tumeric.mp. or exp Curcuma/ (332)
#14 turmeric.mp. or exp Curcuma/ (654)
#15 turmerics.mp. or exp Curcuma/ (320)
#16 tumerics.mp. or exp Curcuma/ (320)
#17 Curcuma zedoaria.mp. or exp Curcuma/ (325)
#18 Curcuma zedoarias.mp. or exp Curcuma/ (320)
#19 zedoaria, Curcuma.mp. or exp Curcuma/ (320)
#20 zedoarias, Curcuma.mp. or exp Curcuma/ (320)
#21 Zedoary zedoaria.mp. or exp Curcuma/ (320)
#22 Zedoary zedoarias.mp. or exp Curcuma/ (320)
#23 zedoaria, Zedoary.mp. or exp Curcuma/ (320)
#24 zedoarias, Zedoary.mp. or exp Curcuma/ (320)
#25 Curcuma longa.mp. or exp Curcuma/ (515)
#26 Curcuma longas.mp. or exp Curcuma/ (320)
#27 Curcuma longas.mp. or exp Curcuma/ (320)
#28 longa, Curcuma.mp. or exp Curcuma/ (321)
#29 longas, Curcuma.mp. or exp Curcuma/ (320)
#30 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (810)
#31 10 and 30 (17)

Chenopodium ambrosioides L.
#1 Osteoarthritis.mp. or exp Osteoarthritis/(34963)
#2 Osteoarthritides.mp. or exp Osteoarthritis/(28841)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/(29335)
#4 Osteoarthroses.mp. or exp Osteoarthritis/(28844)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/(28854)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/(28841)
#7 Degenerative Arthritides.mp. or exp Osteoarthritis/ (28843)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (29215)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (28844)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9(35795)
#11 Chenopodium ambrosioides.mp. or exp Chenopodium ambrosioides/ (13)
#12 Chenopodium ambrosioide.mp. or exp Chenopodium ambrosioides/ (5)
#13 ambrosioide, Chenopodium.mp. or exp Chenopodium ambrosioides/ (5)

#14 ambrosioides, Chenopodium.mp. or exp Chenopodium ambrosioides/ (5)
#15 Wormseed.mp. or exp Chenopodium ambrosioides/ (7)
#16 Wormseeds.mp. or exp Chenopodium ambrosioides/ (5)
#17 Epazote.mp. or exp Chenopodium ambrosioides/ (8)
#18 Epazotes.mp. or exp Chenopodium ambrosioides/ (5)
#19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (15)
#2010 and 19 (0)

Cordia curassavica (Jacq.) Roem. & Schult. (ou *Cordia verbenacea* DC.)
#1 Osteoarthritis.mp. or exp Osteoarthritis/(34963)
#2 Osteoarthritides.mp. or exp Osteoarthritis/(28841)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/(29335)
#4 Osteoarthroses.mp. or exp Osteoarthritis/(28844)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/(28854)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/(28841)
#7 Degenerative Arthritides.mp. or exp Osteoarthritis/ (28843)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (29215)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (28844)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9(35795)
#11 cordia.mp. or exp Cordia/ (32)
#12 cordias.mp. or exp Cordia/ (8)
#13 Manjack.mp. or exp Cordia/ (8)
#14 manjacks.mp. or exp Cordia/ (8)
#15 11 or 12 or 13 or 14 (32)
#16 10 and 15 (0)

Harpagophytum procumbens DC. ex Meisn.

#1 Osteoarthritis.mp. or exp Osteoarthritis/(34963)
#2 Osteoarthritides.mp. or exp Osteoarthritis/(28841)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/(29335)
#4 Osteoarthroses.mp. or exp Osteoarthritis/(28844)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/(28854)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/(28841)
#7 Degenerative Arthritides.mp. or exp Osteoarthritis/ (28843)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (29215)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (28844)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9(35795)
#11 Harpagophytum.mp. or exp Harpagophytum/ (67)
#12 Harpagophytums.mp. or exp Harpagophytum/ (41)
#13 Harpagophytum procumbens.mp. or exp Harpagophytum/ (59)
#14 Harpagophytum procumben.mp. or exp Harpagophytum/ (41)
#15 procumben, Harpagophytum.mp. or exp Harpagophytum/ (41)
#16 Devils Claw.mp. or exp Harpagophytum/ (60)
#17 Claw, Devils.mp. or exp Harpagophytum/ (41)
#18 Claws, Devils.mp. or exp Harpagophytum/ (41)
#19 Devils Claws.mp. or exp Harpagophytum/ (41)
#20 Uncaria procumbens.mp. or exp Harpagophytum/ (41)

#21 Uncaria procumben.mp. or exp Harpagophytum/ (41)
#22 procumben, Uncaria.mp. or exp Harpagophytum/ (41)
#23 procumbens, Uncaria.mp. or exp Harpagophytum/ (41)
#24 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (77)
#25 10 and 24 (28)

Persea gratissima Gaertn.f
#1 Osteoarthritis.mp. or exp Osteoarthritis/(34963)
#2 Osteoarthritides.mp. or exp Osteoarthritis/(28841)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/(29335)
#4 Osteoarthroses.mp. or exp Osteoarthritis/(28844)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/(28854)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/(28841)
#7 Degenerative Arthritides.mp. or exp Osteoarthritis/ (28843)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (29215)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (28844)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9(35795)
#11 persea.mp. or exp Persea/ (118)
#12 perseas.mp. or exp Persea/ (108)
#13 Persea americana.mp. or exp Persea/ (115)
#14 Persea americanas.mp. or exp Persea/ (107)
#15 americana, Persea.mp. or exp Persea/ (107)
#16 americanas, Persea.mp. or exp Persea/ (107)
#17 americanas, Persea.mp. or exp Persea/ (107)
#18 Avocado.mp. or exp Persea/ (286)
#19 Avocado.mp. or exp Persea/ (286)
#20 Avocados.mp. or exp Persea/ (121)
#21 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (308)
#22 10 and 21 (51)

Salix alba L., *Salix daphnoides* Vill, *Salix purpurea* L.
#1 Osteoarthritis.mp. or exp Osteoarthritis/(34963)
#2 Osteoarthritides.mp. or exp Osteoarthritis/(28841)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/(29335)
#4 Osteoarthroses.mp. or exp Osteoarthritis/(28844)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/(28854)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/(28841)
#7 Degenerative Arthritides.mp. or exp Osteoarthritis/ (28843)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (29215)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (28844)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9(35795)
#11 salix.mp. or exp Salix/ (450)
#12 salices.mp. or exp Salix/ (318)
#13 Willow.mp. or exp Salix/ (501)
#14 Willows.mp. or exp Salix/ (343)
#15 Cortex Salicis.mp. or exp Salix/ (318)
#16 Cortex Salici.mp. or exp Salix/ (318)
#17 Salici, Cortex.mp. or exp Salix/ (318)

#18 Salicis, Cortex.mp. or exp Salix/ (319)
#19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (607)
#20 10 and 19 (13)

Uncaria tomentosa (Willd.) DC. e *Uncaria guianensis* (Aubl.) J.F. Gmel.
#1 Osteoarthritis.mp. or exp Osteoarthritis/(34963)
#2 Osteoarthritides.mp. or exp Osteoarthritis/(28841)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/(29335)
#4 Osteoarthroses.mp. or exp Osteoarthritis/(28844)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/(28854)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/(28841)
#7 Degenerative Arthritides.mp. or exp Osteoarthritis/ (28843)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (29215)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (28844)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9(35795)
#11 uncaria.mp. or exp Uncaria/ (84)
#12 Cat Claw.mp. or exp Cat's Claw/ (27)
#13 Cat's Claws.mp. or exp Cat's Claw/ (27)
#14 Cats Claw.mp. or exp Cat's Claw/ (41)
#15 Claw, Cat's.mp. or exp Cat's Claw/ (27)
#16 Claws, Cat's.mp. or exp Cat's Claw/ (27)
#17 Uncaria tomentosa.mp. or exp Cat's Claw/ (40)
#18 Uncaria tomentosas.mp. or exp Cat's Claw/ (27)
#19 tomentosa, Uncaria.mp. or exp Cat's Claw/ (27)
#20 tomentosas, Uncaria.mp. or exp Cat's Claw/ (27)
#21 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (93)
#22 10 and 22 (5)

Zingiber officinale Roscoe.
#1 Osteoarthritis.mp. or exp Osteoarthritis/(34963)
#2 Osteoarthritides.mp. or exp Osteoarthritis/(28841)
#3 Osteoarthrosis.mp. or exp Osteoarthritis/(29335)
#4 Osteoarthroses.mp. or exp Osteoarthritis/(28844)
#5 Arthritis, Degenerative.mp. or exp Osteoarthritis/(28854)
#6 Arthritides, Degenerative.mp. or exp Osteoarthritis/(28841)
#7 Degenerative Arthritides.mp. or exp Osteoarthritis/ (28843)
#8 Degenerative Arthritis.mp. or exp Osteoarthritis/ (29215)
#9 Osteoarthrosis Deformans.mp. or exp Osteoarthritis/ (28844)
#10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9(35795)
#11 ginger.mp. or exp Ginger/ (661)
#12 gingers.mp. or exp Ginger/ (342)
#13 Zingiber officinale.mp. or exp Ginger/ (393)
#14 Zingiber officinales.mp. or exp Ginger/ (338)
#15 officinale, Zingiber.mp. or exp Ginger/ (338)
#16 officinales, Zingiber.mp. or exp Ginger/ (338)
#17 11 or 12 or 13 or 14 or 15 or 16 (689)
#18 10 and 17 (35)

AMED

Harpagophytum procumbens DC. ex Meisn.
#1 exp Osteoarthritis/ or Osteoarthritis.mp. (2780)
#2 exp Osteoarthritis/ or Osteoarthrosis.mp. (2104)
#3 exp Osteoarthritis/ or Osteoarthroses.mp. (2064)
#4 Arthritis, Degenerative.mp. (4)
#5 Arthritides, Degenerative.mp. (0)
6 Degenerative Arthritides.mp. (0)
#7 Degenerative Arthritis.mp. (44)
#8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2853)
#9 exp Harpagophytum/ or Harpagophytum.mp. (51)
#10 exp Harpagophytum/ or Harpagophytums.mp. (11)
#11 Harpagophytum procumbens.mp. (43)
#12 Harpagophytum procumben.mp. (0)
#13 procumbens, Harpagophytum.mp. (3)
#14 exp Harpagophytum/ or Devils Claw.mp. (28)
#15 exp Harpagophytum/ or Claw, Devils.mp. (11)
#16 exp Harpagophytum/ or Devils Claws.mp. (11)
#17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (56)
#18 8 and 17 (14)

Salix alba L., *Salix daphnoides* Vill, *Salix purpurea* L.
#1 exp Osteoarthritis/ or Osteoarthritis.mp. (2780)
#2 exp Osteoarthritis/ or Osteoarthrosis.mp. (2104)
#3 exp Osteoarthritis/ or Osteoarthroses.mp. (2064)
#4 Arthritis, Degenerative.mp. (4)
#5 Arthritides, Degenerative.mp. (0)
6 Degenerative Arthritides.mp. (0)
#7 Degenerative Arthritis.mp. (44)
#8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2853)
#9 exp Salix/ or salix.mp. (29)
#10 Willow.mp. (35)
#11 Willows.mp. (3)
#12 exp Salix/ or salices.mp. (10)
#13 Cortex Salicis.mp. or exp Salix/ (10)
#14 Cortex Salici.mp. or exp Salix/ (10)
#15 Salicis, Cortex.mp. (1)
#16 9 or 10 or 11 or 12 or 13 or 14 or 15 (48)
#17 8 and 16 (5)

Uncaria tomentosa (Willd.) DC. e *Uncaria guianensis* (Aubl.) J.F. Gmel.
#1 exp Osteoarthritis/ or Osteoarthritis.mp. (2780)
#2 exp Osteoarthritis/ or Osteoarthrosis.mp. (2104)
#3 exp Osteoarthritis/ or Osteoarthroses.mp. (2064)
#4 Arthritis, Degenerative.mp. (4)
#5 Arthritides, Degenerative.mp. (0)
6 Degenerative Arthritides.mp. (0)

#7 Degenerative Arthritis.mp. (44)
#8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2853)
#9 exp Uncaria/ or uncaria.mp. (70)
#10 Cat Claw.mp. (0)
#11 Cat's Claws.mp. (0)
#12 Cats Claw.mp. (19)
#13 Claw, Cat's.mp. (0)
#14 Uncaria tomentosa.mp. (35)
#15 Uncaria tomentosas.mp. (1)
#16 tomentosa, Uncaria.mp. (1)
#17 tomentosas, Uncaria.mp. (0)
#18 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (80)
#19 8 and 18 (4)

Curcuma longa L. (ou *Curcuma domestica* Valeton)
#1 exp Osteoarthritis/ or Osteoarthritis.mp. (2780)
#2 exp Osteoarthritis/ or Osteoarthrosis.mp. (2104)
#3 exp Osteoarthritis/ or Osteoarthroses.mp. (2064)
#4 Arthritis, Degenerative.mp. (4)
#5 Arthritides, Degenerative.mp. (0)
6 Degenerative Arthritides.mp. (0)
#7 Degenerative Arthritis.mp. (44)
#8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2853)
#9 exp Curcuma/ or curcuma.mp. (182)
#10 exp Curcuma/ or curcumas.mp. (101)
#11 tumeric.mp. or exp Curcuma longa/ (58)
#12 tumerics.mp. or exp Curcuma longa/ (54)
#13 turmeric.mp. or exp Curcuma longa/ (102)
#14 turmerics.mp. or exp Curcuma longa/ (54)
#15 Curcuma zedoaria.mp.(11)
#16 Curcuma zedoarias.mp. (0)
#17 zedoaria, Curcuma.mp. (1)
#18 exp Curcuma longa/ or curcuma longa.mp. (106)
#19 exp Curcuma longa/ or curcuma longas.mp. (54)
#20 longa, Curcuma.mp. or exp Curcuma/ (101)
#21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (205)
#228 and 21 (5)

Cordia curassavica (Jacq.) Roem. & Schult. (ou *Cordia verbenacea* DC.)
#1 exp Osteoarthritis/ or Osteoarthritis.mp. (2780)
#2 exp Osteoarthritis/ or Osteoarthrosis.mp. (2104)
#3 exp Osteoarthritis/ or Osteoarthroses.mp. (2064)
#4 Arthritis, Degenerative.mp. (4)
#5 Arthritides, Degenerative.mp. (0)
6 Degenerative Arthritides.mp. (0)
#7 Degenerative Arthritis.mp. (44)
#8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2853)
#9 cordia.mp. (26)

#10 Cordias.mp. (0)
#11 9 or 10 (26)
#12 8 and 11 (0)

Boswellia serrata Roxb. ex Colebr
#1 exp Osteoarthritis/ or Osteoarthritis.mp. (2780)
#2 exp Osteoarthritis/ or Osteoarthrosis.mp. (2104)
#3 exp Osteoarthritis/ or Osteoarthroses.mp. (2064)
#4 Arthritis, Degenerative.mp. (4)
#5 Arthritides, Degenerative.mp. (0)
6 Degenerative Arthritides.mp. (0)
#7 Degenerative Arthritis.mp. (44)
#8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2853)
#9 exp Boswellia/ or Boswellia.mp. (58)
#10 Boswellia serrata.mp. (29)
#11 Boswellia carteri.mp. (3)
#12 Boswellia carterii.mp. (9)
#13 9 or 10 or 11 or 12 (58)
#14 8 and 13 (7)

Zingiber officinale Roscoe.
#1 exp Osteoarthritis/ or Osteoarthritis.mp. (2780)
#2 exp Osteoarthritis/ or Osteoarthrosis.mp. (2104)
#3 exp Osteoarthritis/ or Osteoarthroses.mp. (2064)
#4 Arthritis, Degenerative.mp. (4)
#5 Arthritides, Degenerative.mp. (0)
6 Degenerative Arthritides.mp. (0)
#7 Degenerative Arthritis.mp. (44)
#8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2853)
#9 exp Zingiber officinale/ or Ginger.mp. (169)
#10 exp Zingiber officinale/ or Gingers.mp. (86)
#11 exp Zingiber officinale/ or Zingiber officinale.mp. (140)
#12 exp Zingiber officinale/ or Zingiber officinales.mp. (85)
#13 officinale, Zingiber.mp. (1)
#14 9 or 10 or 11 or 12 or 13 (192)
#15 8 and 14 (12)

Chenopodium ambrosioides L.
#1 exp Osteoarthritis/ or Osteoarthritis.mp. (2780)
#2 exp Osteoarthritis/ or Osteoarthrosis.mp. (2104)
#3 exp Osteoarthritis/ or Osteoarthroses.mp. (2064)
#4 Arthritis, Degenerative.mp. (4)
#5 Arthritides, Degenerative.mp. (0)
6 Degenerative Arthritides.mp. (0)
#7 Degenerative Arthritis.mp. (44)
#8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2853)
#9 Chenopodium ambrosioides.mp. (16)
#10 Chenopodium ambrosioide.mp. (0)

#11 ambrosioides, Chenopodium.mp. (1)
#12 9 or 10 or 11 (16)
#13 8 and 12 (0)

Persea gratissima Gaertn.f
#1 exp Osteoarthritis/ or Osteoarthritis.mp. (2780)
#2 exp Osteoarthritis/ or Osteoarthrosis.mp. (2104)
#3 exp Osteoarthritis/ or Osteoarthroses.mp. (2064)
#4 Arthritis, Degenerative.mp. (4)
#5 Arthritides, Degenerative.mp. (0)
6 Degenerative Arthritides.mp. (0)
#7 Degenerative Arthritis.mp. (44)
#8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2853)
#9 Persea.mp. (16)
#10 Perseas.mp. (0)
#11 Persea americana.mp. (9)
#12 Persea americanas.mp. (0)
#13 americana, Persea.mp. (0)
#14 Avocados.mp. (0)
#15 9 or 10 or 11 or 12 or 13 or 14 (16)
#16 8 and 15 (0)

Bowdichia virgilioides Kunth
#1 exp Osteoarthritis/ or Osteoarthritis.mp. (2780)
#2 exp Osteoarthritis/ or Osteoarthrosis.mp. (2104)
#3 exp Osteoarthritis/ or Osteoarthroses.mp. (2064)
#4 Arthritis, Degenerative.mp. (4)
#5 Arthritides, Degenerative.mp. (0)
6 Degenerative Arthritides.mp. (0)
#7 Degenerative Arthritis.mp. (44)
#8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2853)
#9 bowdichia.mp. (3)
#10 8 and 9 (0)

LILACS

Bowdichia virgilioides Kunth
(tw:(Osteoarthritis)) AND (tw:(bowdichia)) (0)

Boswellia serrata Roxb. ex Colebr
(tw:(Osteoarthritis)) AND (tw:(broswellia)) (0)

Curcuma longa L. (ou *Curcuma domestica* Valeton)
(tw:(Osteoarthritis)) AND (tw:(curcuma)) (0)

Chenopodium ambrosioides L.
(tw:(Osteoarthritis)) AND (tw:(chenopodium)) (0)

Cordia curassavica (Jacq.) Roem. & Schult. (ou *Cordia verbenacea* DC.)
(tw:(Osteoarthritis)) AND (tw:(cordia)) (0)

Harpagophytum procumbens DC. ex Meisn.
(tw:(Osteoarthritis)) AND (tw:(Harpagophytum)) (1)

Persea gratissima Gaertn.f
(tw:(Osteoarthritis)) AND (tw:(persea)) (0)

Salix alba L., *Salix daphnoides* Vill, *Salix purpurea* L.
(tw:(Osteoarthritis)) AND (tw:(salix)) (0)

Uncaria tomentosa (Willd.) DC. e *Uncaria guianensis* (Aubl.) J.F. Gmel.
(tw:(Osteoarthritis)) AND (tw:(uncaria)) (0)

Zingiber officinale Roscoe.
(tw:(Osteoarthritis)) AND (tw:(ginger)) (0)

The Brazilian thesis database (CAPES)

Boswellia serrata Roxb. ex Colebr
“Osteoarthritis" and “Boswellia” (1)

Bowdichia virgilioides Kunth
“Osteoarthritis" and “Bowdichia” (18)

Curcuma longa L. (ou *Curcuma domestica* Valeton)
“Osteoarthritis" and “Curcuma” (16)

Chenopodium ambrosioides L.
“Osteoarthritis" and “Chenopodium” (38)

Cordia curassavica (Jacq.) Roem. & Schult. (ou *Cordia verbenacea* DC.)
“Osteoarthritis" and “Cordia” (19)

Harpagophytum procumbens DC. ex Meisn.
“Osteoarthritis" and “Harpagophytum” (1)

Persea gratissima Gaertn.f
“Osteoarthritis" and “Persea” (17)

Salix alba L., *Salix daphnoides* Vill, *Salix purpurea* L.
“Osteoarthritis" and “Salix” (4)

Uncaria tomentosa (Willd.) DC. e *Uncaria guianensis* (Aubl.) J.F. Gmel.
“Osteoarthritis" and “Uncaria” (7)

Zingiber officinale Roscoe.
"Osteoarthritis" and "Ginger" (1)

CLINICAL TRIAL. GOV

Boswellia serrata Roxb. ex Colebr
"Osteoarthritis" and "boswellia" (2)

Bowdichia virgilioides Kunth
"Osteoarthritis" and "bowdichia" (0)

Curcuma longa L. (ou *Curcuma domestica* Valeton)
"Osteoarthritis" and "curcuma" (3)

Chenopodium ambrosioides L.
"Osteoarthritis" and "Chenopodium" (1)

Cordia curassavica (Jacq.) Roem. & Schult. (ou *Cordia verbenacea* DC.)
"Osteoarthritis" and "cordia" (0)

Harpagophytum procumbens DC. ex Meisn.
"Osteoarthritis" and "harpagophytum" (1)

Persea gratissima Gaertn.f
"Osteoarthritis" and "persea" (0)

Salix alba L., *Salix daphnoides* Vill, *Salix purpurea* L.
"Osteoarthritis" and "salix" (4)

Uncaria tomentosa (Willd.) DC. e *Uncaria guianensis* (Aubl.) J.F. Gmel.
"Osteoarthritis" and "uncaria" (0)

Zingiber officinale Roscoe.
"Osteoarthritis" and "ginger" (1)

WHO TRIAL REGISTER

Boswellia serrata Roxb. ex Colebr
#1 Osteoarthritis AND Boswellia (0)

Bowdichia virgilioides Kunth
#1 Osteoarthritis AND Bowdichia (0)

Curcuma longa L. (ou *Curcuma domestica* Valeton)
#1 Osteoarthritis AND curcuma (0)

Chenopodium ambrosioides L.
#1 Osteoarthritis AND Chenopodium (0)

Cordia curassavica (Jacq.) Roem. & Schult. (ou *Cordia verbenacea* DC.)
#1 Osteoarthritis AND cordia (0)

Harpagophytum procumbens DC. ex Meisn.
#1 Osteoarthritis AND Harpagophytum (0)

Persea gratissima Gaertn.f
#1 Osteoarthritis AND Persea (0)

Salix alba L., *Salix daphnoides* Vill, *Salix purpurea* L.
#1 Osteoarthritis AND salix (0)

Uncaria tomentosa (Willd.) DC. e *Uncaria guianensis* (Aubl.) J.F. Gmel.
#1 Osteoarthritis AND uncaria (0)

Zingiber officinale Roscoe.
#1 Osteoarthritis AND ginger (0)

APÊNDICE D – Características dos estudos incluídos

Bierget et al., 2004

Methods	Randomised, double-blind, Placebo control and active control, 3 parallel, multicentre trial, wash-out phase of 4 10 days, no addicional analgesics, NSAIDs or systemic corticosteroids during study, all patients received regular physical therapy, duration 6 weeks.
Participants	Randomised n=127, Completed n=106, Mean age 62yrs. M:F 53:74. Inclusion criteria: osteoarthritis the hip or of the knee (ACR criteria or score Kellgren e Lawrence), WOMAC > 30mm.
Interventions	Willow bark extract (Salix daphnoides cortex) 1572,96mg (2 x 2 x 393,24mg, equivalent to 240mg salicin), Placebo control tablets (ingredients not reported), Active control tablets, Diclofenac 100mg (2 x 2 x 25mg).
Otcomes	WOMAC questionnaire, SF-36, assesment by patient, assesment by physician, adverse event reported.
Notes	Results equivocal.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised in block of six, computer generated randon number sequence.
Allocation concealment (selection bias)	Low risk	Author confirms information "assessors and patient were blinded to the allocation".
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind, author makes it clear that the tablets was identical.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals, included intention-to-treat and protocol analysis.
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but the study included all the desired outcomes. Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria or score Kellgren e Lawrence.

Bliddal et al., 2000

Methods	Randomised, double-blind, Placebo control, Active control, 3 group corssover, wash-out phase of 7 days, no addicional analgesics, NSAIDs or systemic corticosteroids during study, rescue medicine permitted (acetominophen - 3000mg daily), duration 12 weeks.
Participants	Randomised n=67, Completed n=56, Mean age 66yrs. M:F 15:41. Inclusion criteria: osteoarthritis the hip or of the knee (ACR criteria or score Kellgren e Lawrence).
Interventions	Zingiber officinale extract (Eurovita EXT 33) 510mg (3 x 170mg), Placebo control tablets (ingredients not reported), Active control tablets, ibuprofen 400mg.
Outcomes	Pain VAS, Lequesne Index, use rescue medicine, daily ain diary (4 poin scale), adverse event reported.
Notes	Results favour ibuprofen over ginger, ginger over placebo.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomised in blook of six, method of randomisation incompletely reported.
Allocation concealment (selection bias)	High risk	Method of alocation incompletely reported.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind, author makes it clear that the tablets was identical.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals, protocol analysis only.
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but the study included all the desired outcomes. Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria or score Kellgren e Lawrence.

Chantre et al., 2000

Methods	Randomised, double-blind, Active control, 2 parallel groups, Multicentre trial, no addicional analgesics, NSAIDs or systemic corticosteroids during study, rescue medicine permitted (diclofenac and/or paracetamol with cafeine),
Participants	Randomised n=122, Completed n=92, Mean age 61yrs. M:F 45:77. Inclusion criteria: osteoarthritis the hip or of the knee (ACR criteria or score Kellgren e Lawrence).
Interventions	Harpagophytum procumbens extract 2610mg (6 x 435mg) equilavent to 60mg harpagoside, Active control tablets, diacerhein 100mg (2 x 50mg).

Outcomes	Pain VAS, Lequesne Index, assesment by patient, use rescue medicine, adverse event reported.
Notes	Results indicate H procumbens equally effective as diacerhein on pain, function and Lequesne index.

Risk of bias table

Bias	Authors' judgement	Supportforjudgement
Random sequence generation (selection bias)	High risk	Randomised in blook of four, method of randomisation incompletely reported.
Allocation concealment (selection bias)	High risk	Method of alocation incompletely reported.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals, included intention-to-treat and protocol analysis.
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but the study included all the desired outcomes. Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria or score Kellgren e Lawrence.

Haghighi et al., 2005

Methods	Randomised, duble-blind, placebo control and Active control, 3 parallel groups, single centre trial, no addicional analgesics, NSAIDs or systemic corticosteroids during study, rescue medicine permitted (paracetamol, duration 1 month.
Participants	Randomised n=120, no withdrawals, Mean age 58,5yrs. M:F 31:89. Inclusion criteria: osteoarthritis the hip or of the knee (criteria not specified).
Interventions	Zingiber officinale tablets 1000mg (2 x 500mg) equilavent to 30mg extract, Active control tablets (Ibuprofen 1200mg - 3 x 400mg), placebo control tablets (ingredients not reported).
Outcomes	Pain (VAS), Gelling or regressive pain after rising, Joint swelling scores, Joint motion slope scores, adverse event reported.
Notes	Results indicate Ginger extract equally effective as ibuprofen but and both are

Risk of bias table

Bias	Authors' judgement	Supportforjudgement

Random sequence generation (selection bias)	High risk	Method of randomisation incompletely reported, Author described "randomised" only.
Allocation concealment (selection bias)	High risk	Method of alocation incompletely reported.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported 100% compliance, no withdrawals.
Selective reporting (reporting bias)	High risk	Adverse events not reported.
Other bias	High risk	Criteria for diagnosis of OA not specified.

Kimmatkar et al., 2003

Methods	Randomised, double-blind, Placebo control, 2 group crossover, Single centre trial, washout 7 days, no addicional analgesics, NSAIDs or systemic corticosteroids during study, currently using physiotherapy, duration 19 weeks (2 x 8 interventions + 3 week washout).
Participants	Randomised n=30, Completed n=30. No withdrawals. Mean age 59yrs. M:F 12:18. Inclusion criteria: osteoarthritis knee (criteria not specified).
Interventions	Boswellia serrata extract (Cap Wokvel) 1000mg (3 x 333mg) with 40% boswellic acid, Placebo control (starch powder).
Outcomes	Pain VAS, loss of function, swelling, adverse event reported.
Notes	Results favour intervention.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised in one of two groups, computer generated ramdon number sequence.
Allocation concealment (selection bias)	Low risk	Author confirms information.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind
Incomplete outcome data (attrition bias)	Low risk	Reported 100% compliance, no withdrawals.
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but the study included all the desired outcomes. Reported adverse events.

Other bias	High risk	Criteria for diagnosis of OA not specified.

Kuptniratsaikul et al., 2009

Methods	Randomised, single-blind, active control, 2 parallel, Single centre trial, no addicional analgesics, NSAIDs or systemic corticosteroids during study, duration 6 weeks.
Participants	Randomised n=107, Completed n=91. Mean age 61yrs. M:F 12:18. Inclusion criteria: osteoarthritis knee (ACR criteria or score Kellgren e Lawrence).
Interventions	Curcuma domestica 2000mg (4 x 500mg) with 1000mg curcuminoids, Active control: ibuprofen 800mg (2 x 400mg).
Outcomes	Pain on level walking, Pain on stair climbing, 100m walk, satisfaction with treatment (questionaire), adverse event reported.
Notes	Efficacy of Curcuma domestica is not significantly different from active control.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Described as ramdomised but method incompletely reported: "computerized randomization code was kept by a research assistant".
Allocation concealment (selection bias)	Low risk	Author confirms information.
Blinding of participants and personnel (performance bias)	High risk	Described as single-blind.
Blinding of outcome assessment (detection bias)	High risk	Described as single-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals, included protocol analysis only.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria or score Kellgren e Lawrence.

Kuptniratsaikul et al., 2014

Methods	Randomised to one of two groups (random number sequence), double-blind, Active control, 2 parallel groups, Multicentre tria, no addicional analgesics, NSAIDs or systemic corticosteroids during study, tramadol as a rescue medication, duration 4 weeks.
Participants	Randomised n=367, Completed n=331. Mean age 60.5yrs. M:F 296:71. Inclusion criteria: osteoarthritis knee (ACR criteria or score Kellgren e Lawrence).

Interventions	Curcuma domestica 1500mg (6 x 250mg) with 1000mg curcuminoids, Active control: ibuprofen 1200mg (6 x 200mg).
Outcomes	Pain, stiffness, and function (WOMAC), 6-minute walk distance, satisfaction with treatment (questionaire), adverse event reported.
Notes	C. domestica extracts were as efficacious as ibuprofen in pain reduction and functional improvement.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised of number was generated by computerized method.
Allocation concealment (selection bias)	Low risk	Author confirms information "allocation codes were serially concealed in paque envelops".
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals, included protocol analysis only.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria or score Kellgren e Lawrence.

Lardos et al., 2004

Methods	Randomised, double-blind, Active control, Placebo control, 3 parallel groups, Single centre trial, washout 3 days, no addicional analgesics, NSAIDs or systemic corticosteroids during study, duration 3 weeks.
Participants	Randomised n=79, Completed n=78. Mean age 64yrs. Inclusion criteria: osteoarthritis the hip or of the knee (criteria not specified).
Interventions	Group 1= willow bark 90mg, group 2= willow bark 180mg, group 3= diclofenac 50mg (3 x 50mg).
Outcomes	Pain, physical function, stiffnes, assesment by patient, assesment by physician (4 poin scale), adverse events.
Notes	Results equivocal.

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	High risk	Randomised, method of randomisation incompletely reported.
Allocation concealment (selection bias)	High risk	Author confirms information, but details of allocation not provided.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but the study included all the desired outcomes. Reported adverse events.
Other bias	High risk	Criteria for diagnosis of OA not specified.

Madhu et al., 2013

Methods	Randomised, single-blind, Active control, Placebo control, 4 parallel groups, Single centre trial, no addicional analgesics, NSAIDs or systemic corticosteroids during study, duration 6 weeks.
Participants	Randomised n=120, Completed n=110. Mean age 57yrs. Inclusion criteria: osteoarthritis knee (ACR criteria or score Kellgren e Lawrence).
Interventions	Group 1= Placebo (cellulose), group 2= NR-INF-02 (500 mg/capsule), group 3= GS (375 mg/capsule), group 4= NR-INF-02 (500 mg/capsule) + GS (375 mg/capsule).
Outcomes	Pain (VAS), physical function, stiffnes, (WOMAC) assesment by patient, adverse events, total number of rescue medications consumed.
Notes	Results favour intervention.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, computer-generated simple randomization sequence.
Allocation concealment (selection bias)	Low risk	Described "box containing either placebo or intervention".
Blinding of participants and personnel (performance bias)	High risk	Described as single-blind.
Blinding of outcome assessment (detection bias)	High risk	Described as single-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.

Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria or score Kellgren e Lawrence.

Paramdeep, 2013

Methods	Randomised, open trial, Active control, 3 parallel groups, Single centre trial, duration 12 weeks
Participants	Randomised n=60, Completed n= not reported. Mean age 53yrs. M:F 20:40. Inclusion criteria: osteoarthritis knee (ACR criteria or score Kellgren e Lawrence).
Interventions	Group 1= Diclofenac 50 mg and Cap. placebo, group 2= Ginger 750 mg and Cap. placebo, group 3= Ginger 750 mg and Tab. Diclofenac 50 mg.
Outcomes	Pain (VAS - WOMAC), adverse events, total number of rescue medications consumed.
Notes	Results equivocal.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomised, method of randomisation incompletely reported.
Allocation concealment (selection bias)	High risk	Described "box containing either placebo or intervention".
Blinding of participants and personnel (performance bias)	High risk	Open trial.
Blinding of outcome assessment (detection bias)	High risk	Open trial.
Incomplete outcome data (attrition bias)	Low risk	Reported 100% compliance, no withdrawals.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria or score Kellgren e Lawrence.

Piscoya e Herman, 1997

Methods	Randomised, Placebo control, 2 parallel groups, Multicentre trial, duration 4 week.
Participants	Randomised n=45, Completed n=45 (intervention 30, control 15). No withdrawals. Mean age 60.5 yrs. Inclusion criteria: osteoarthritis knee (ACR criteria).
Interventions	Uncaria guianensis extract 100mg, Placebo control (ingredient not reported).
Outcomes	Pain at rest, pain activity,pain at night, assesment by patient, assesment by physician, adverse event questionnaire.
Notes	Results favour intervention.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Described randomised, method not reported.
Allocation concealment (selection bias)	High risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported 100% compliance, no withdrawals.
Selective reporting (reporting bias)	Low risk	Reported adverse events
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Piscoya et al., 2001

Methods	Randomised, Placebo control, 2 parallel groups, Multicentre trial, duration 4 week.
Participants	Randomised n=45, Completed n=45 (intervention 30, control 15). No withdrawals. Mean age 60 yrs. All male. Inclusion criteria: osteoarthritis knee (ACR criteria).
Interventions	Uncaria guianensis extract 100mg (freeze-dried), Placebo control (ingredient not reported).
Outcomes	Pain at rest, pain activity, pain at night, assesment by patient, assesment by physician, adverse event questionnaire.
Notes	Results favour intervention.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Described randomised, method not reported.
Allocation concealment (selection bias)	High risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.

Incomplete outcome data (attrition bias)	Low risk	Reported 100% compliance, no withdrawals.
Selective reporting (reporting bias)	High risk	Adverse events not reported.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Shimid et al., 2001

Methods	Randomised, Placebo control, 2 parallel, single centre trial, wash-out phase of 4 6 days with placebo, no addicional analgesics, NSAIDs or systemic corticosteroids during study, all patients received regular physical therapy, duration 2 weeks.
Participants	Randomised n=78, Completed n=68, Mean age 53 yrs. M:F 59:19. Inclusion criteria: osteoarthritis the hip or of the knee (ACR criteria), clinical, laboratory and radiographic.
Interventions	Willow bark extract tablets (Salix purpurea e salix daphnoides) 1360mg (2 x 2 x 340mg, equivalent to 240mg salicin), Placebo control tablets (celulose and lactose).
Outcomes	WOMAC questionnaire, assesment by patient, assesment by physician, adverse event reported.
Notes	Results favour intervention.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised in blocks of four, computer generated ramdon number sequence.
Allocation concealment (selection bias)	Low risk	Author confirms information, but details of allocation not provided.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals, included intention-to-treat and protocol analysis.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Sontakke et al., 2007

Methods	Randomised, Open trial, active control, 2 parallel, single centre trial,use rescue medicine (ibuprofen up to 1200mg), duration 7 months (6 months intervention, 1 month follow up).
Participants	Randomised n=66, Completed n=57, Age 40-70yrs. Inclusion criteria: osteoarthritis knee (ACR criteria).
Interventions	Boswellia serrada extract tablets 999mg (3 x 333mg, with 65% organic acids), Active control tablets (Valdecoxib) 10mg.
Outcomes	WOMAC questionnaire, pain, stiffines, physical function, adverse event.
Notes	Results reported to favour intervention for WOMAC pain subscale only. Result favour control on all other outcomes.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised in two groups, SAS system for Windows.
Allocation concealment (selection bias)	High risk	Open trial.
Blinding of participants and personnel (performance bias)	High risk	Open trial.
Blinding of outcome assessment (detection bias)	High risk	Open trial.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals, included intention-to-treat and protocol analysis.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Wigler et al., 2003

Methods	Randomised to one of two groups (random numbers sequence), double-blind, Placebo control, 2 group crossover, wash-out phase of 4 days, use rescue medicine (paracetamol), duration 48,5 weeks (4 days run-in, 2 x 12 weeks crossover, 24 weeks open follow-up).
Participants	Randomised n=29, Completed stage 1 n=24, completed stage 2 n=20, completed stage 3 n=17. Mean age 62 yrs. Inclusion criteria: osteoarthritis knee (ACR criteria).
Interventions	Zingiber officinale extract tablets 1000mg (4 x 250mg,equivalent 40mg glicerol), Placebo control tablets (maltodextrin only).
Outcomes	WOMAC, knee circumference, adverse event.
Notes	Results equivocal stage 1, in stage 2 and 3 favour intervention.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised in one of two groups, computer generated ramdon number sequence.
Allocation concealment (selection bias)	Low risk	Author confirms information, but details of allocation not provided.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Zakeri et al., 2011

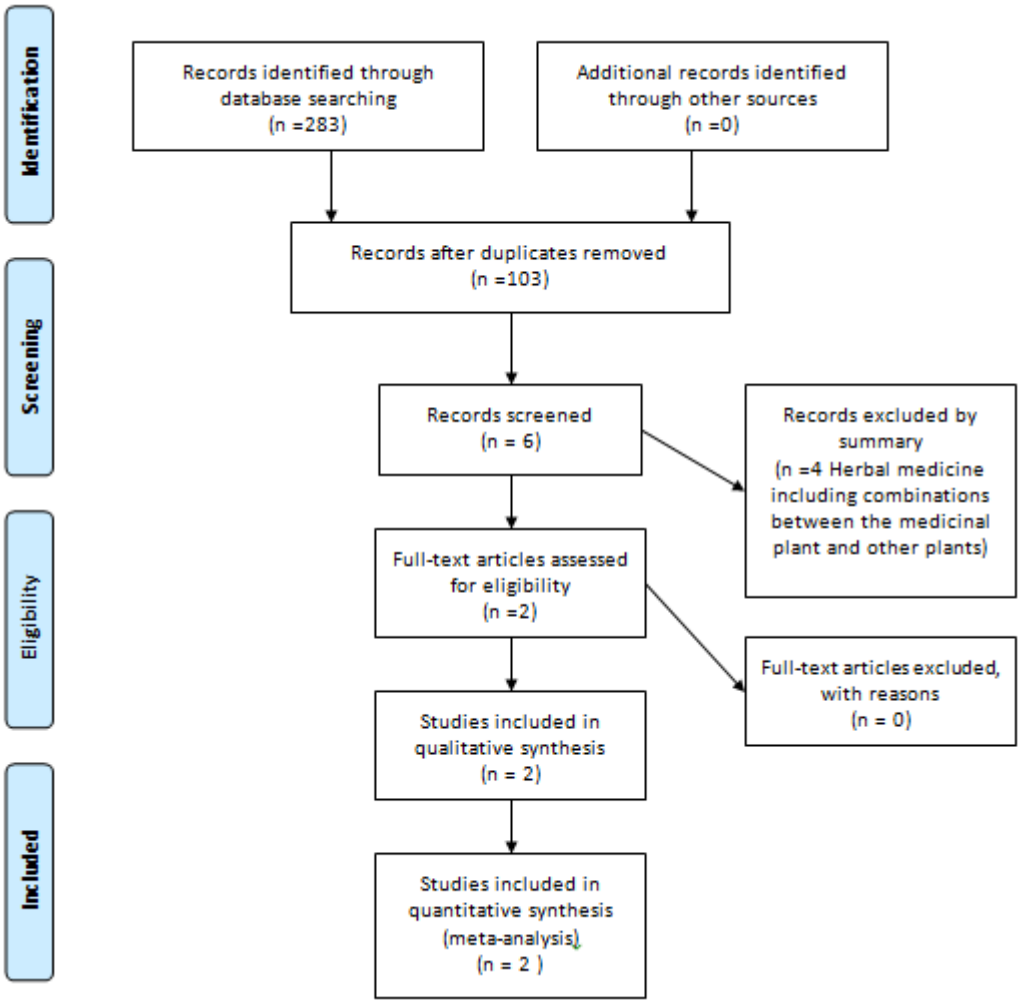
Methods	Randomised, double-blind, Placebo control, single centre trial, wash-out phase of 7 days, use rescue medicine (paracetamol and aspirin), some kinds of knee exercises were taught to all patients and they were recommended to perform the knee exercises 3 times a day, each time including 15 repetitions of each exercise, duration 6 weeks.
Participants	Randomised n=320, Completed n=204. Mean age 47yrs. Inclusion criteria: osteoarthritis knee (ACR criteria).
Interventions	Zingiber officinale extract tablets 500mg (2 x 250mg), Placebo control tablets (ingredient not reported).
Outcomes	VAS** (100 mm) on standing, VAS (100 mm) after 50 m walking, pain (WOMAC), stiffines (WOMAC), physical function(WOMAC), adverse event.
Notes	

Risk of bias table

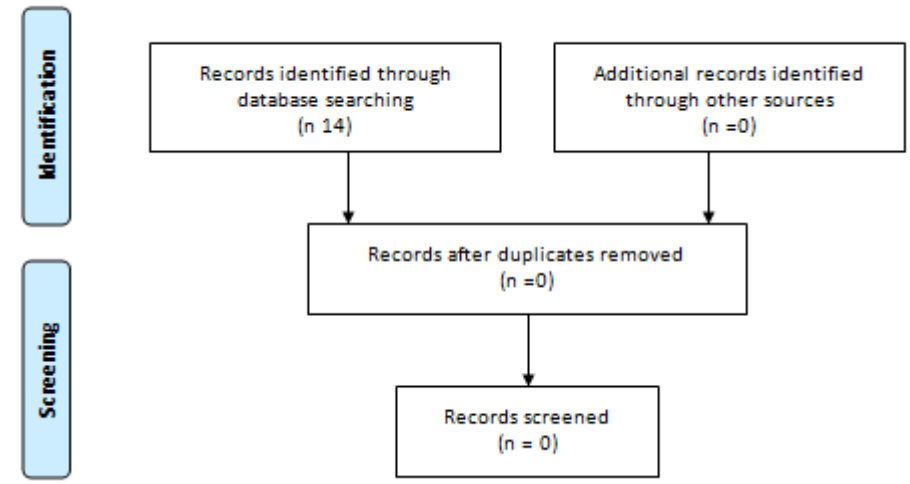
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of randomisation incompletely reported, Author described "randomised" only.
Allocation concealment (selection bias)	High risk	Author confirms information, but details of allocation not provided.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.

Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals, protocol analysis.
Selective reporting (reporting bias)	High risk	Adverse events not reported.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

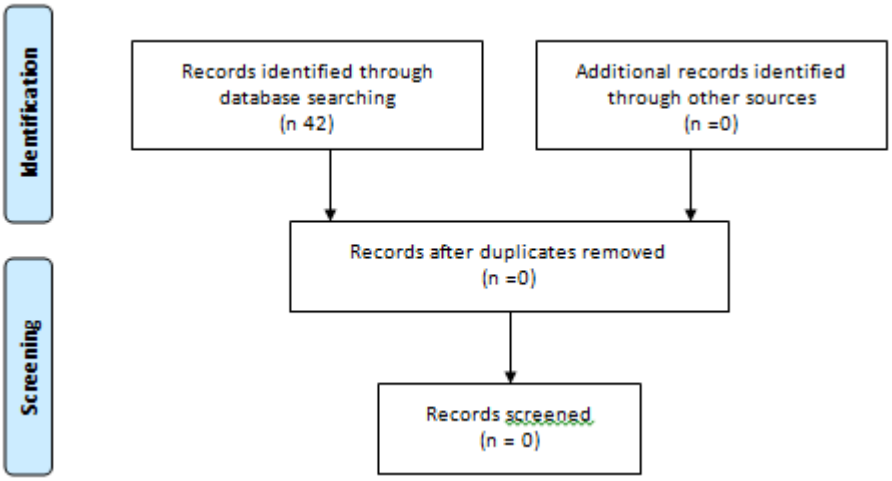
APÊNDICE E – Fluxograma *Boswellia serrata Roxb. ex Colebr*



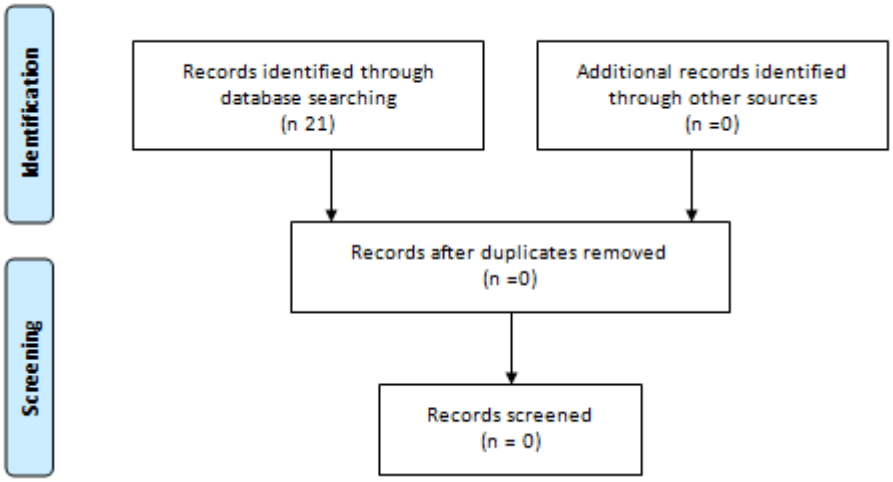
APÊNDICE F – Fluxograma *Bowdichia virgilioides Kunth*



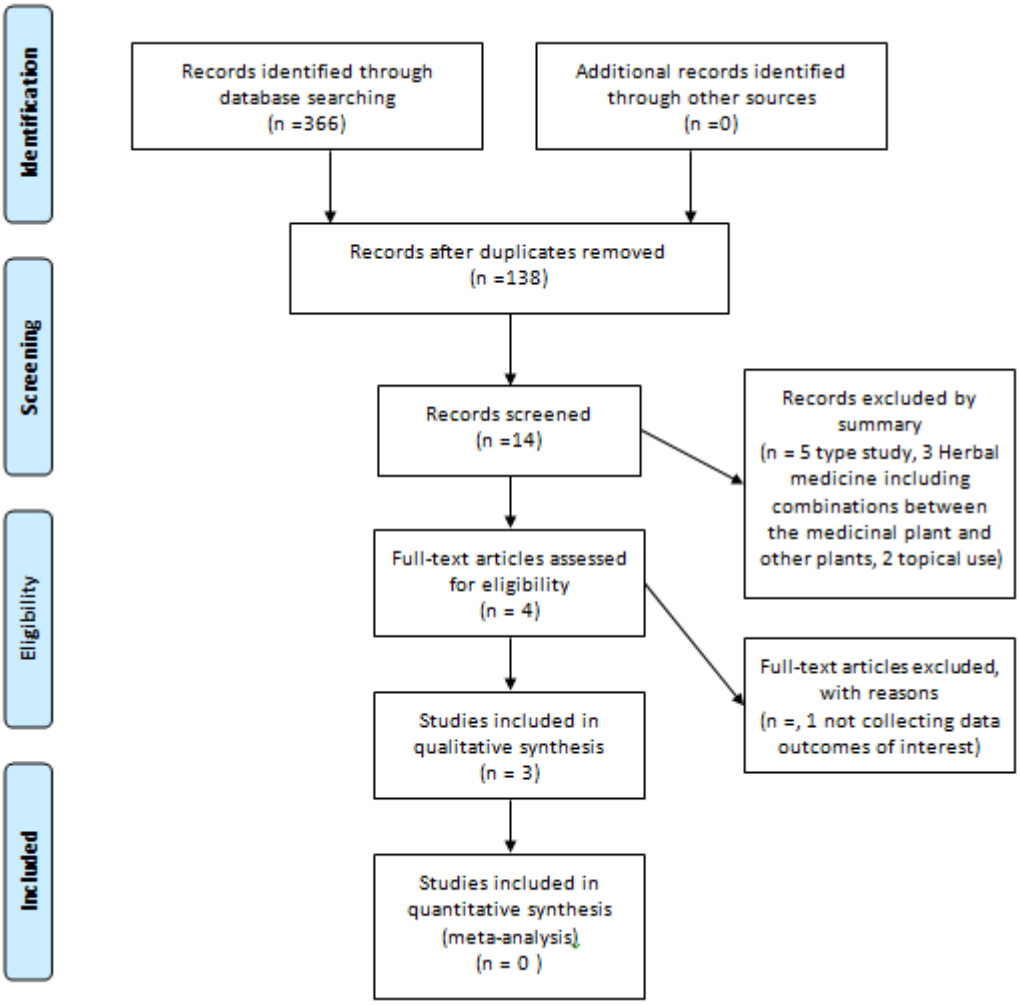
APÊNDICE G – Fluxograma *Chenopodium ambrosioides L*



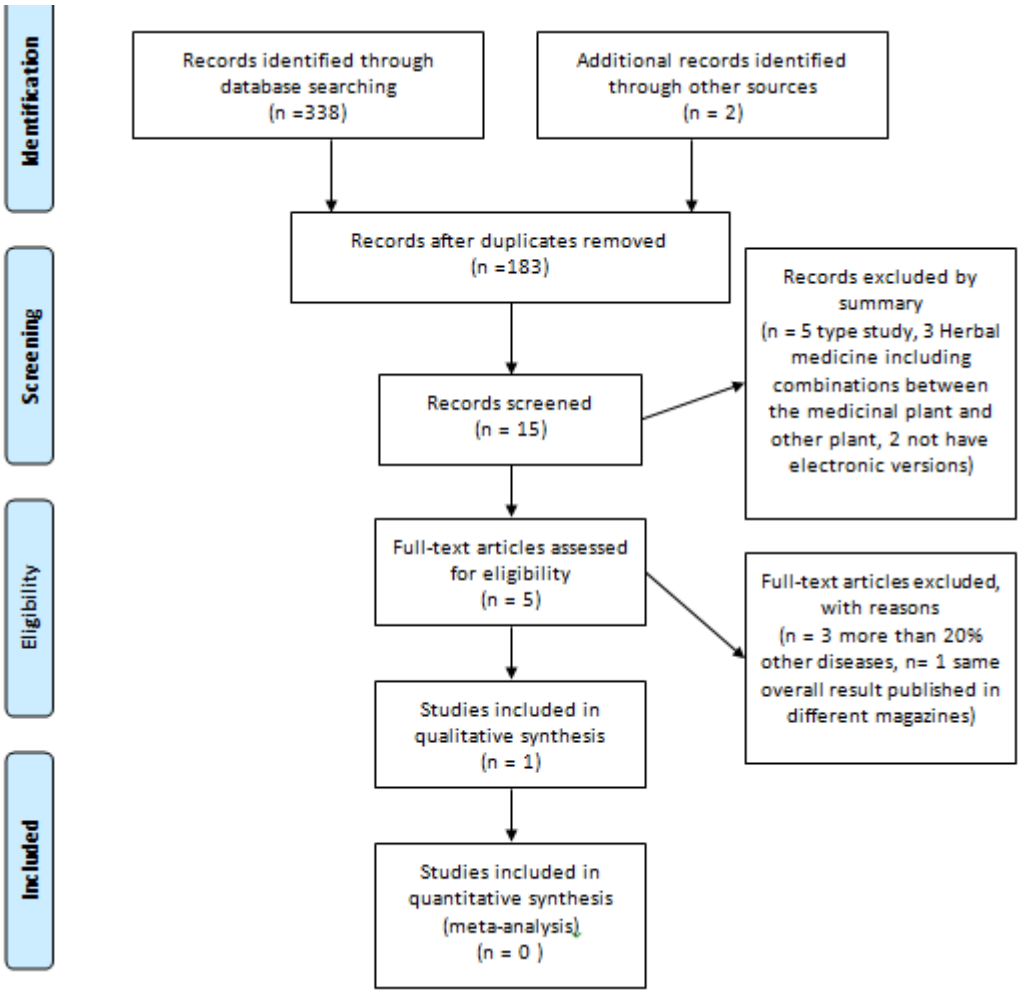
APÊNDICE H – Fluxograma *Cordia curassavica (Jacq.) Roem. & Schult*



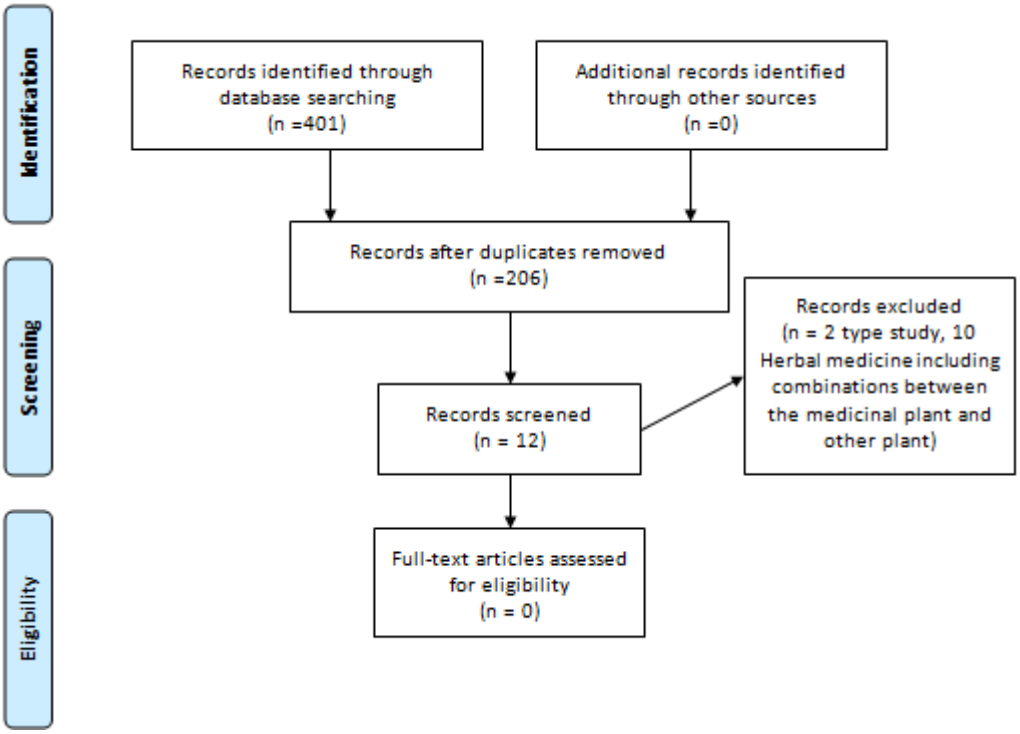
APÊNDICE I – Fluxograma *Curcuma longa L. (ou Curcuma domestica Veleton)*



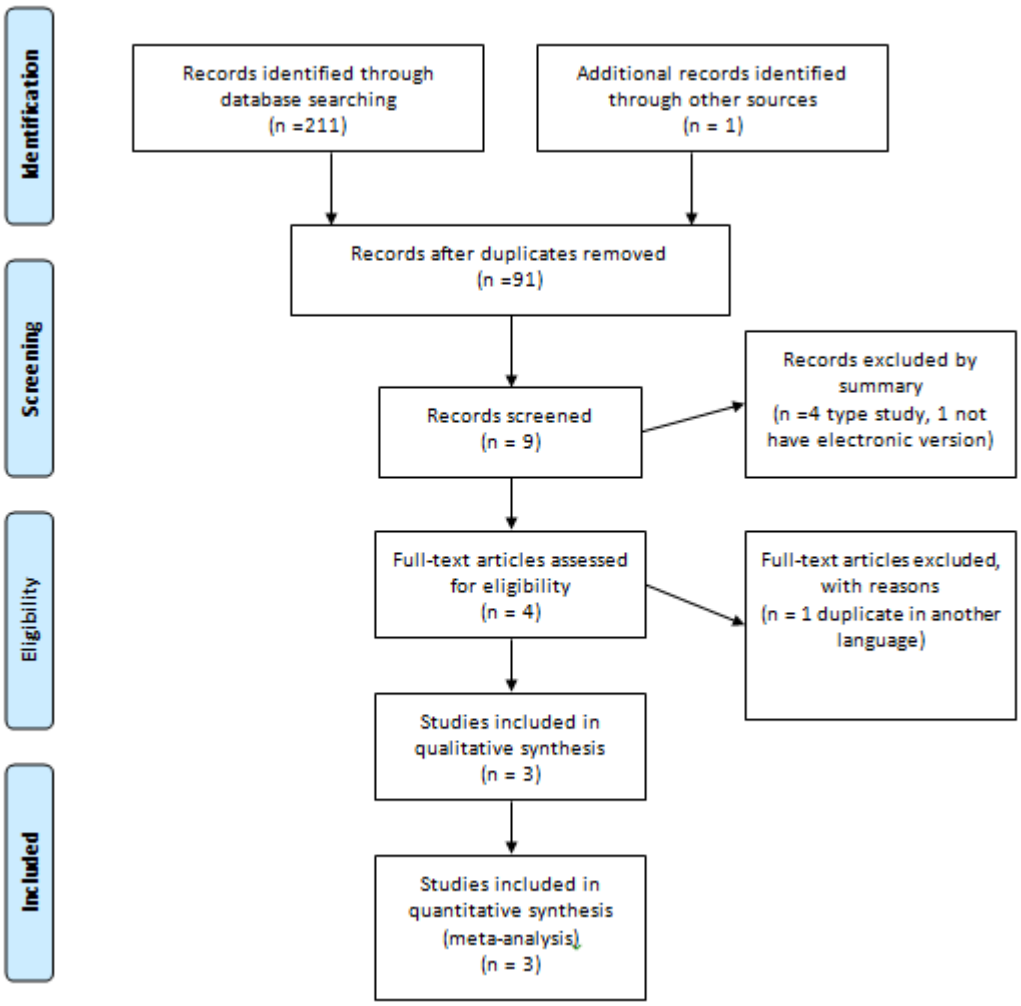
APÊNDICE J – Fluxograma *Harpagophytum procumbens DC*



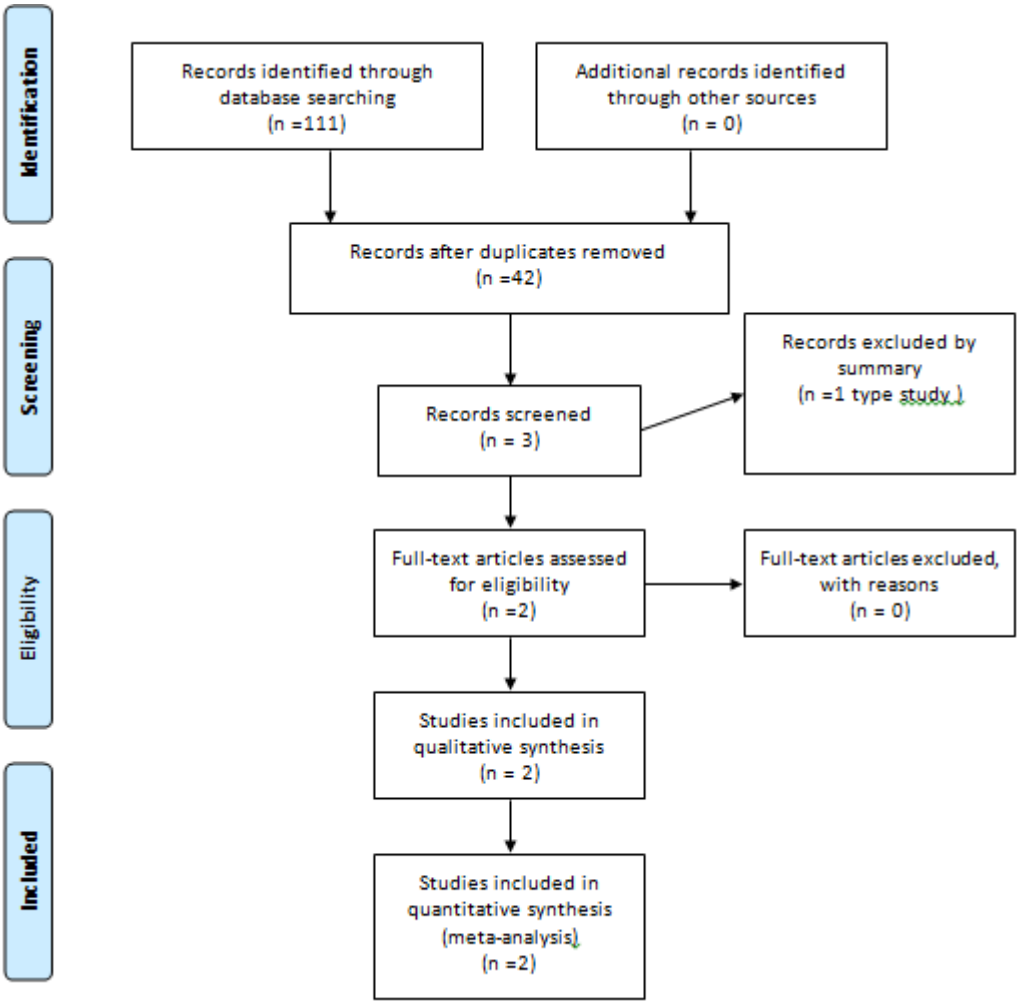
APÊNDICE K – Fluxograma *Persea gratissima Gaertn.f. (or Persea americana Mill.)*



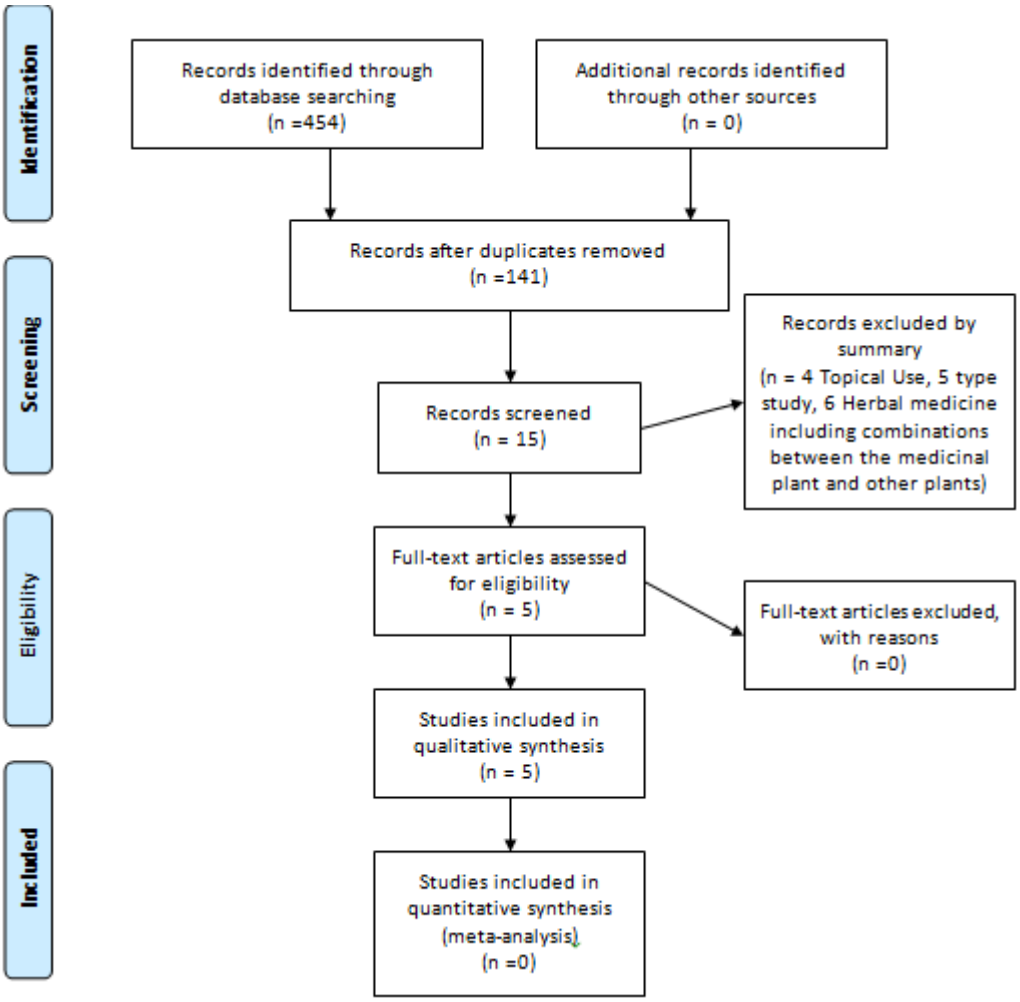
APÊNDICE L – Fluxograma *Salix alba L.; Salix daphnoides Vill; Salix purpurea*



APÊNDICE M – Fluxograma *Uncaria tomentosa (Willd.) DC; Uncaria guianensis (Aubl.) J.F. Gmel*



APÊNDICE N – FLUXOGRAMA *Zingiber officinale Roscoe.*



APÊNDICE O: REFERÊNCIA DOS ESTUDOS INCLUÍDOS NA REVISÃO SISTEMÁTICA

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