

THE ANALYSIS STUDY OF ASSOCIATION OF PHARMACOLOGICAL TREATMENTS WITH LONG-TERM PAIN CONTROL IN PATIENTS WITH KNEE OSTEOARTHRITIS : A COMPREHENSIVE SYSTEMATIC REVIEW

*^{1,2}Yosie Yulanda Putra, ^{2,3}Deby Tri Lestari, ^{2,4}Zikri Saputra, ¹Bella Merisa Liona

¹Mayjen H.A. Thalib Regional General Hospital, Jambi, Indonesia

²Faculty of Medicine, University of Jambi, Indonesia

³Rimbo Medika General Hospital, Jambi, Indonesia

⁴Pertamedika Baiturrahim General Hospital, Jambi, Indonesia

Corresponding Author:
yosieputra.y@gmail.com

ABSTRACT

Background: Knee osteoarthritis (KOA) is a degenerative joint disease affecting 10% of males and 13% of women aged 60 or older. It causes joint discomfort, weakened muscles, and physical limitations. Treatment consists of surgical and non-surgical approaches, with knee arthroplasty being the most successful. Non-regenerative therapies like ozone, corticosteroids, and prolotherapy are popular but short-lived. Chinese herbal medicine (CHM) is widely used to treat KOA, targeting specific biological processes associated with the disease.

Methods: Following PRISMA 2020 guidelines, this systematic review concentrated on full-text English literature published between 2014 and 2024. Editorials and review articles that appeared in the same journal as the submission were not accepted without a DOI. A number of websites, including ScienceDirect, PubMed, and SagePub, were utilized to gather the literature.

Result: The study looked at more than 200 publications using reputable sources including Science Direct, SagePub, and PubMed. After it was decided that eight publications needed greater investigation, a more extensive review of the entire literature was carried out.

Conclusion: Knee osteoarthritis is a common disease affecting middle-aged and elderly individuals. Platelet-rich plasma (PRP) injections, combined with hyaluronic acid, can alleviate knee pain and improve function. However, the efficacy varies depending on the formulation. Traditional Chinese herbal medicine has shown potential in treating KOA, but its effectiveness and safety remain debatable due to limited clinical trials and methodological rigor.

Keyword: KOA, knee, joint, CHM, PRP

INTRODUCTION

Knee osteoarthritis (KOA) is a prevalent degenerative joint disease that affects 10% of males and 13% of women aged 60 or older.¹ Several risk factors contribute to KOA, including age, gender, obesity, joint injuries from work or sports, and geographic location. KOA can lead to joint discomfort, weakened muscles, physical limitations, and a lower quality of life. Long-term pain may also result in anxiety, depression, and cognitive impairment, further impacting social and economic well-being.^{2,3} KOA is a complex and progressive joint disease, accounting for over half of all cases of osteoarthritis worldwide. With the aging population and increasing obesity rates, the prevalence of KOA is expected to rise significantly.^{4,5}

Treatment for KOA typically involves a combination of surgical and non-surgical approaches, with the choice of treatment based on the patient's individual circumstances, activity level, joint alignment, and disease progression.⁶ Knee arthroplasty has historically been the most successful treatment for KOA, although it is irreversible.⁴ The rate of total knee arthroplasty (TKA) in the US has doubled from 1991 to 2010 and is projected to continue to rise. TKA is recommended when non-surgical treatments fail to halt disease progression or when KOA-related pain worsens.⁶ However, the high cost of surgical or medical interventions is a significant concern. In certain cases, KOA can be managed without surgery. Therapeutic goals for KOA include preventing disease progression and alleviating pain, with two main types of treatments available: regenerative and non-regenerative.⁴

The benefits of non-surgical therapies, such as ozone, corticosteroids (CS), prolotherapy (PRL), hyaluronic acid (HA), and prolotherapy (PRL), on KOA development and pain, have been well-studied.⁷ Patients with KOA experience significant clinical pain and poor physical functioning, and therapies that are often prescribed (such as opioids and non-steroidal anti-inflammatory medications) have both long-term dangers and minimal benefits.⁸ Their outcomes, meanwhile, have fallen short of the original expectations. Patients with KOA are frequently treated with HA and CS, which are regarded as the gold standard for managing KOA pain. These treatments frequently have short-lived effects and only offer momentary alleviation; they do not address the underlying cause of the condition. Because CS suppresses the immune system, it might exacerbate joint injury if given excessively long or in large dosages.^{7,9} As a result, treating KOA with complementary and alternative therapy is becoming more and more popular among physicians and patients.¹⁰

Chinese herbal medicine (CHM) has been widely used in China and around the world to treat knee osteoarthritis (KOA) in various ways.¹¹ The use of CHM for pain disorders, including KOA, has been steadily increasing globally and in Asian countries.¹² Unlike other herbal remedies, CHM contains unique medicinal ingredients that target specific biological processes associated with the disease, depending on the manifestation of particular symptoms.¹⁰ A recent study has found that CHM has analgesic, blood circulation-boosting, and anti-inflammatory properties that actively alleviate pain. While CHM has been a crucial part of KOA treatment in China and is gaining popularity abroad, there is currently limited quantitative research data on its impacts. Its biological mechanisms and potential interactions with other prescription drugs are yet to be fully understood.¹³ Two systematic reviews have deemed CHM as safe and effective in treating KOA. However, there is a knowledge gap regarding its specific use due to poor study quality and small sample sizes. The recent increase in high-quality randomized controlled clinical trials (RCTs) examining the effectiveness and safety of CHM in treating KOA is promising.¹⁰ Understanding the relationship between pharmacologic medications and knee osteoarthritis can aid in developing effective treatment regimens. This systematic literature review aimed to explore the relationship between pharmacologic therapies and long-term pain management in knee osteoarthritis patients, based on research conducted over the past decade.

METHODS

PROTOCOL

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards were closely followed by the study's author to ensure compliance with all regulations. To provide accurate and persuasive research findings, a well-considered approach was used.

CRITERIA FOR ELIGIBILITY

This study provides an extensive overview of research conducted in the past 10 years regarding the connection between long-term pain management and pharmacologic treatments for osteoarthritis in the knee. Through in-depth data analysis, this program seeks to explain and enhance patient care procedures. The primary objective of this thesis is to draw attention to significant topics that are present in a variety of literary works.

To ensure the accuracy of the data used in this analysis, strict inclusion and exclusion criteria were implemented. Anything that has been published in English between 2014 and 2024 is eligible for inclusion. Exclusion criteria include published reviews, editorials, submissions without a DOI, and multiple entries in the same publication.

SEARCH STRATEGY

The study's keywords include "knee osteoarthritis, pharmacologic, KOA, pharmacology, long-term, pain control, reliever, outcomes, therapy". For this research, the following Boolean MeSH keywords were entered into the databases: (((“knee osteoarthritis”[MeSH Terms] OR “knee osteoarthritis”[All Fields] AND “pharmacologic”[All Fields]) OR (“knee

OA"[MeSH Terms] OR "KOA"[All Fields] AND "pharmacology"[All Fields]) AND ("long-term"[MeSH Terms] OR "pain control"[All Fields] OR "pain"[All Fields] OR "reliever"[MeSH Subheading] OR "outcomes"[All Fields] OR "therapy"[All Fields]))).

DATA RETRIEVAL

Before beginning this in-depth study, the writers carefully examined how relevant each article was based on its title and abstract. Only studies that met the article's objectives and inclusion criteria were granted more weight. A clear and consistent pattern emerged after multiple searches. English was the only language authorized for full-text submissions. The most rigorous screening process yielded content that directly related to the study's topic and satisfied all predetermined inclusion criteria. Research that failed to satisfy these requirements was usually disregarded and their findings were not given much weight. The evaluation contained a wide range of data, including factors, titles, authors, publication dates, locations, and study processes.

QUALITY ASSESSMENT AND DATA SYNTHESIS

The authors themselves go over each article's abstract and title carefully to determine which ones require further investigation. Afterward, each document that was initially up for review had to be thoroughly inspected. The evaluation results guided the selection of the review papers. This criterion made it possible to choose papers for further analysis more quickly, which in turn made it possible to evaluate earlier research and the circumstances surrounding its evaluation more thoroughly.

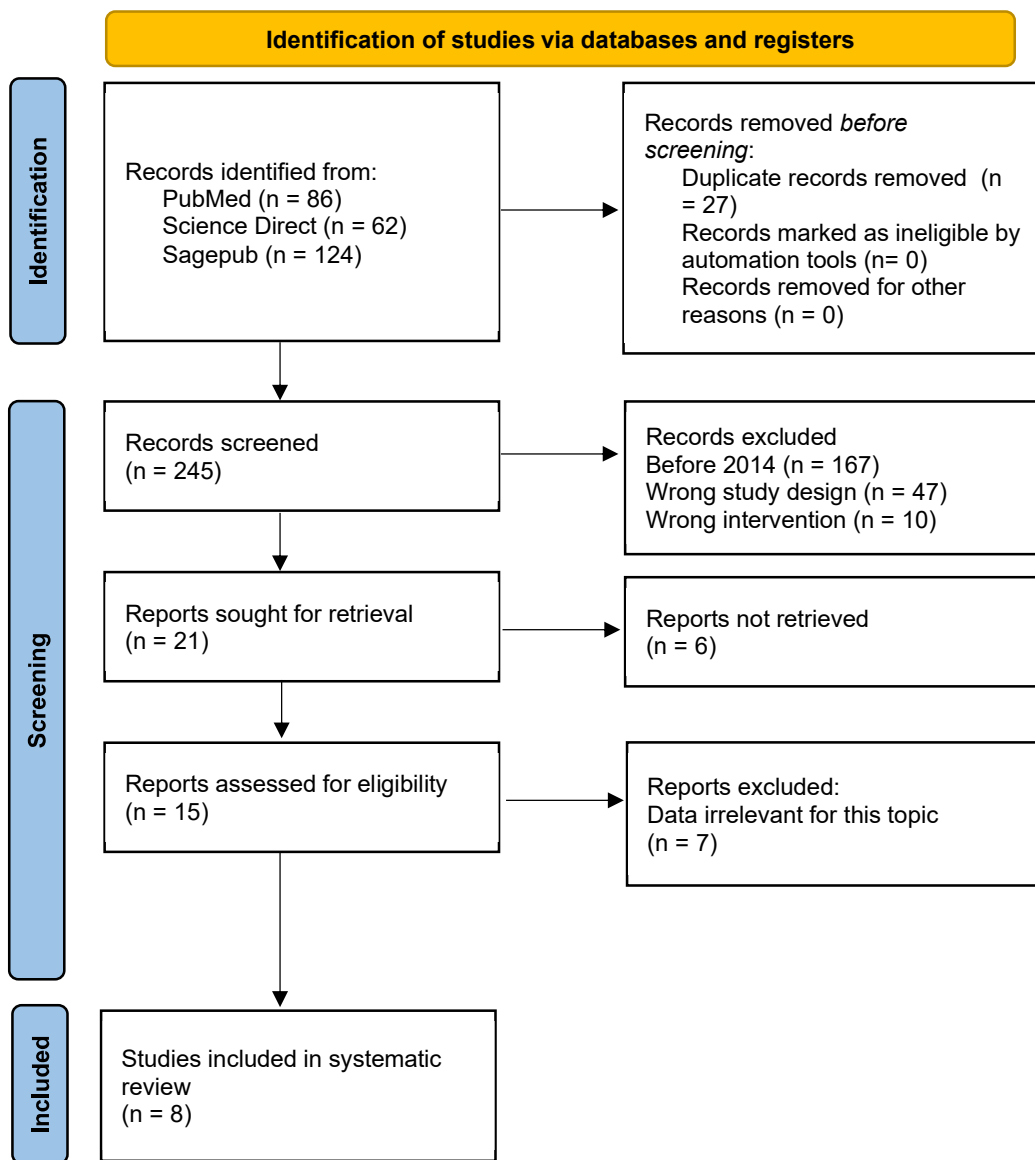


Figure 1. Article search flow chart

RESULT

Our team started the investigation by meticulously compiling a substantial collection of publications from reliable sources including Science Direct, PubMed, and SagePub. We picked eight papers that were deemed extremely relevant to our current systematic investigation after a rigorous three-stage screening process. Following that, we narrowed down certain subjects for more study and carefully assessed each report. To help you speed our investigation, we have provided a brief overview of the assessed content in Table 1.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Zhao et al.¹⁴ (2020)	China	Systematic Review	7 studies	Studies involving 941 patients found that PRP combined with HA was more effective in reducing knee pain in the VAS comparison after 6 months. PRP combined with HA also improved WOMAC Function Score and WOMAC Total Score at the 12-month follow-up. In terms of AEs, PRP combined with HA was not significantly different from PRP or HA alone.
Huang et al.¹⁵ (2022)	China	Systematic Review	18 studies	A study involving 1512 participants found that the treatment group of Zhengqing Fengtongning release tablet (ZQFTN) had lower pain scores, stiffness, and function scores compared to the control group. The total effective rate was higher relative risk, but there was no significant difference in the incidence of adverse reactions between the two groups. The study suggests that ZQFTN treatment may be a potential treatment option for osteoarthritis.
Lin et al.¹⁰ (2022)	China	Systematic Review	56 studies	CHM treatment significantly reduces VAS, WOMAC, and Lequesne index in patients with KOA, improving the Lysholm score and total effective rate. This treatment has fewer adverse effects, indicating its safety and well-tolerance, and has been shown to be effective in treating KOA.
Zhao et al.¹⁶ (2022)	China	Meta Analysis	17 studies	The study analyzed 17 clinical trials, involving 1930 participants. Results showed that the Jinwu Gutong (JWGT) group showed better efficacy than the Western drug group in reducing WOMAC score, VAS score, KSS score, IL-6, and TNF- α . The effective rate and incidence of adverse reactions were lower in the JWGT group. JWGT +NSAIDs had more advantages in efficacy

				and reducing adverse reactions.
Campbell et al.¹⁷ (2023)	USA	RCT	37 patients	The study observed no significant analgesic effects on clinical pain severity or physical functioning in patients with knee osteoarthritis. The combination of dronabinol and hydromorphone showed minimal benefit, but subjective drug effects and HAP ratings increased.
Crowley & Soti¹ (2023)	USA	Systematic Review	14 studies	KOA therapy, using PRP, is effective in treating the disease by alleviating pain, enhancing joint function, increasing range of motion, and improving mobility. However, studies with higher platelet concentrations failed to show significant improvements. Further investigation is needed to modify the disease's progression.
Mintarjo et al.¹⁸ (2023)	Indonesia	Review	-	Osteoarthritis is a chronic degenerative disease causing joint damage and osteophytes formation. Symptoms include joint pain, deformity, and inflammation. Management methods include regeneration and non-regeneration therapies, including physiotherapy and injections.
Zeng et al.¹⁹ (2023)	China	Meta Analysis	12 studies	Patients were treated with diacerein, a treatment that effectively reduced pain indicators like WOMAC and VAS. Diacerein outperformed NSAIDs in global efficacy assessment and sustained effectiveness at four weeks post-treatment. There was no significant difference in adverse events incidence between the diacerein and NSAID groups, but the GRADE evaluation indicated low evidence quality.

Zhao et al. conducted a study on PRP, a blood product derived from patients' whole blood, and its results showed that the treatment of KOA was effective. The study included 7 studies, with the results indicating that differences in PRP concentrations may impact the efficacy of treating KOA. The results highlight the importance of understanding the potential benefits of PRP in treating KOA.¹⁴

Huang's studies showed the strength of ZQFTN in relieving knee pain, stiffness, and daily activity disorders, reducing inflammatory factors, and improving clinical response rate without increasing adverse reactions. However, quality limitations need further confirmation.¹⁵

Lin's study demonstrates that CHM, either as an adjuvant or monotherapy, effectively reduces VAS, WOMAC, and Lequesne index in patients with KOA. CHM is well-tolerated and safe, potentially contributing to the formulation of a

herbal formula for further clinical use. However, larger multicenter, high-quality RCTs are needed to validate CHM's benefits.¹⁰

Zhao's 2022 study showed that JWGT, when combined with NSAIDs, HA, or GS, significantly improves the clinical efficacy of KOA treatment, demonstrating its effectiveness and safety in treating KOA.¹⁶

Campbell's study examines the combined effects of dronabinol and hydromorphone on chronic pain patients. The results show that dronabinol alone does not improve hydromorphone's analgesic profile, but it increases side effects and adverse events. The hydromorphone's effects are more significant, negating the enhancement of analgesia by dronabinol.¹⁷

Crowley & Soti's research on KOA suggests that PRP treatment, a type of PRP therapy, can alleviate pain, improve joint function, and increase mobility in KOA patients, though further research is needed to determine optimal concentration levels.¹

Mintarjo et al.'s study highlights the diverse therapeutic modalities available for patients with knee osteoarthritis, emphasizing the importance of comprehensive treatment to achieve satisfactory results, as each patient's condition is unique and requires tailored treatment based on individual symptoms and severity.¹⁸

Zeng's study suggests that diacerein, a pharmacological agent, may have significant efficacy in treating KOA patients, offering an alternative treatment strategy for those contraindicated by NSAIDs. Further high-quality studies and longer follow-up are needed for informed decisions.¹⁹

DISCUSSION

KOA, a common disease affecting middle-aged and elderly individuals, poses challenges to their physical and mental health.²⁰ The cause of KOA is still unknown, and there is a lack of effective conservative treatments.²¹ Clinicians are particularly interested in intra-articular injection of PRP or HA for KOA.^{1,14} Platelet-rich plasma (PRP) injections are promising for KOA treatment. Several randomized studies have shown that PRP therapy is safe and effective. Although IA PRP is not yet a standard treatment for KOA, it is more successful than HA in young, active people with low-grade OA.¹⁸ PRP extracts platelets from the patient's blood and releases macrophages and growth factors, which are beneficial for articular cartilage repair and regeneration.¹⁴ PRP can stimulate the formation of the extracellular matrix and improve metabolic balance to aid in tissue healing.²² Hyaluronic acid (HA), a high molecular weight polysaccharide, promotes the synthesis of natural HA, delaying further joint disease. Studies have indicated that PRP combined with HA can alleviate knee pain and improve KOA patients' function. However, the VAS score at 6 months after treatment indicated that intra-articular injection of PRP combined with HA relieved pain in patients with KOA. This study is the first systematic evaluation of the efficacy and safety of PRP combined with HA compared with PRP or HA alone for KOA.¹⁴ However, the effectiveness of PRP treatment varies depending on the formulation used. Studies using WOMAC and VAS, pain and function indices, and other modalities like pain questionnaires or functional tests have shown mixed results. Some studies have also explored the effect of PRP on cartilage thickness, with some claiming no effect and others showing significant maintenance of cartilage. Understanding the mechanism through which KOA progresses and the etiology of the disease is crucial for a more targeted approach to treatment. Future studies should focus on elucidating the mechanism through which KOA manifests and progresses, allowing for a more targeted approach to treatment. This will help researchers express clinical relevancy more clearly and contextualize the seemingly vague similarities between the studies.¹

The study by Campbell et al. evaluated the effects of co-administering dronabinol (10mg) and hydromorphone (4mg) on evoked and clinical pain, self-reported drug effects, human abuse potential (HAP) metrics, physical and cognitive functioning, and adverse events (AEs) in patients with chronic pain. The findings revealed limited clinical benefits, suggesting that co-administering dronabinol (10mg) with hydromorphone (4mg) to this clinical population demonstrated a slightly enhanced risk for use along with elevated risk for AEs in the combined condition. The findings were consistent across the sexes and were consistent across sexes.¹⁷ Campbell et al. found that hydromorphone+dronabinol was associated with significant analgesia on several QST outcomes, but it was not different than hydromorphone by itself, indicating no added benefit of the combination at the doses tested. None of the drug conditions significantly changed ratings of clinical pain severity.¹⁷ These findings are consistent with previous laboratory studies with healthy adults demonstrating limited additive benefits of combined cannabinoids and opioids on analgesia.^{23,24} The study is the first to evaluate the individual and combined effects of dronabinol and hydromorphone on clinically relevant standardized physical testing measures.²⁵ None of the drug conditions improved or diminished these outcomes, which may be related to the null effects observed for clinical pain severity. Longer-term follow-up with those who co-use these drugs may shed further light on understanding their relative HAP and side effects of co-use.¹⁷

In a study conducted by Zeng et al., the effectiveness of diacerein in the treatment of knee osteoarthritis patients was evaluated, with a focus on WOMAC score, VAS score, and overall efficacy judgments. The results indicated that diacerein showed significant efficacy in improving WOMAC and VAS scores, comparable to NSAIDs. Interestingly, both patients and investigators perceived diacerein to be notably more effective than NSAIDs in terms of overall efficacy. Furthermore, the study revealed that diacerein outperformed NSAIDs in enhancing WOMAC and VAS scores during the follow-up period after the treatment, suggesting a stronger long-term effect.¹⁹ KOA is predominantly characterized by cartilage

degeneration, with pro-inflammatory cytokines playing a pivotal role in the development of the condition.²⁶ Diacerein, an anthraquinone derivative, functions by inhibiting the IL-1 system and its associated downstream signaling pathways, leading to the reduction of IL-1 β activation and promoting cartilage repair. Additionally, it inhibits the MAPK pathway activated by IL-1 and the binding of transcription factors NF-kappaB and AP-1.^{27,28} Diacerein has demonstrated promising therapeutic potential in treating KOA, especially in elderly patients and those at a higher risk for gastrointestinal bleeding and cardiovascular disease. The incidence of adverse events associated with diacerein was similar to that of NSAIDs, indicating a favorable safety profile.¹⁹

A study conducted a meta-analysis of the use of traditional Chinese herbal medicine in treating knee osteoarthritis patients. The analysis included 56 high-quality randomized controlled trials (RCTs) involving 5350 patients. The findings indicated that CHM, either used as an adjuvant therapy or monotherapy, led to a reduction in pain and improved function in KOA patients. CHM was also found to have fewer adverse effects compared to control treatments, suggesting its safety and effectiveness in treating KOA.¹⁰ Previous studies have also demonstrated the safety and effectiveness of oral and topical use of CHM in relieving pain, restoring function, and promoting health in KOA patients.²⁹ Additionally, ZQFTN, an oral preparation of *Sinomenium acutum*, was found to effectively alleviate knee pain, morning stiffness, and daily activity disturbance in KOA patients.³⁰ It also demonstrated a higher clinical effectiveness rate compared to the control group, indicating its significant clinical efficacy as a complementary and alternative medicine (CAM) for KOA. The use of ZQFTN did not increase the risk for adverse events and was deemed safe as a CAM for KOA.¹⁵

However, the effectiveness and safety of other treatments such as duhuo Jisheng decoction (DJD) and orally bioavailable avocado soybean unsaponifiable (ASU) remain debatable due to limited clinical trials and methodological rigor.³¹ Another study focused on the use of Jinwu Gutong (JWGT) in combination with conventional Western medicine for treating KOA. The findings suggested that JWGT, either alone or combined with Western medicine, improved clinical treatment effectiveness, reduced adverse reactions, increased Knee Society Score (KSS), and reduced pain and inflammation markers. However, the study identified some shortcomings in the meta-analysis, such as heterogeneity in outcome indicators and inconsistencies in measurement time points. The study recommended using internationally recognized research outcome indicators and increasing research cooperation among different clinical centers for future research on JWGT.¹⁶

CONCLUSION

KOA, a common disease affecting middle-aged and elderly individuals, presents challenges to their physical and mental health. Platelet-rich plasma (PRP) injections are promising for KOA treatment, extracting platelets from the patient's blood and releasing macrophages and growth factors. Studies have shown that PRP combined with hyaluronic acid (HA) can alleviate knee pain and improve KOA patients' function. However, the efficacy of PRP treatment varies depending on the formulation used. A study by Campbell et al. evaluated the effects of co-administering dronabinol (10mg) and hydromorphone (4mg) on evoked and clinical pain, self-reported drug effects, human abuse potential (HAP) metrics, physical and cognitive functioning, and adverse events (AEs). Diacerein showed significant efficacy in improving WOMAC and VAS scores, comparable to NSAIDs. A meta-analysis of traditional Chinese herbal medicine (CHM) in treating knee osteoarthritis (KOA) patients found that CHM led to a reduction in pain and improved function in KOA patients, with fewer adverse effects compared to control treatments. However, the effectiveness and safety of other treatments such as duhuo Jisheng decoction (DJD) and orally bioavailable avocado soybean unsaponifiable (ASU) remain debatable due to limited clinical trials and methodological rigor.

REFERENCES

- [1] Crowley, J. L., & Soti, V. (2023). Platelet-Rich Plasma Therapy: An Effective Approach for Managing Knee Osteoarthritis. *Cureus*, 15(12), e50774. <https://doi.org/10.7759/cureus.50774>
- [2] Hamood, R., Tirosh, M., Fallach, N., Chodick, G., Eisenberg, E., & Lubovsky, O. (2021). Prevalence and Incidence of Osteoarthritis: A Population-Based Retrospective Cohort Study. *Journal of clinical medicine*, 10(18), 4282. <https://doi.org/10.3390/jcm10184282>
- [3] Sen R, Hurley JA. Osteoarthritis. [Updated 2023 Feb 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482326/>
- [4] Wu, Z., Zhou, R., Zhu, Y., Zeng, Z., Ye, Z., Wang, Z., Liu, W., & Xu, X. (2022). Self-Management for Knee Osteoarthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Pain research & management*, 2022, 2681240. <https://doi.org/10.1155/2022/2681240>
- [5] Arslan, I. G., Damen, J., de Wilde, M., van den Driest, J. J., Bindels, P. J. E., van der Lei, J., Schiphof, D., & Bierma-Zeinstra, S. M. A. (2022). Incidence and Prevalence of Knee Osteoarthritis Using Codified and Narrative Data From Electronic Health Records: A Population-Based Study. *Arthritis care & research*, 74(6), 937–944. <https://doi.org/10.1002/acr.24861>
- [6] Cram, P., Lu, X., Kates, S. L., Singh, J. A., Li, Y., & Wolf, B. R. (2012). Total knee arthroplasty volume, utilization, and outcomes among Medicare beneficiaries, 1991–2010. *JAMA*, 308(12), 1227–1236. <https://doi.org/10.1001/2012.jama.11153>
- [7] Pradelli, L., Sinigaglia, T., Migliore, A., Checchia, G. A., Franceschi, F., Frediani, B., Iannone, F., & Romanini, E. (2021). Non-Surgical Treatment of Knee Osteoarthritis: Multidisciplinary Italian Consensus on Best Practice. *Therapeutics and clinical risk management*, 17, 507–530. <https://doi.org/10.2147/TCRM.S288196>

- [8] Michael, J. W., Schlüter-Brust, K. U., & Eysel, P. (2010). The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. *Deutsches Arzteblatt international*, 107(9), 152–162. <https://doi.org/10.3238/arztebl.2010.0152>
- [9] Wee, T. C., Neo, E. J. R., & Tan, Y. L. (2021). Dextrose prolotherapy in knee osteoarthritis: A systematic review and meta-analysis. *Journal of clinical orthopaedics and trauma*, 19, 108–117. <https://doi.org/10.1016/j.jcot.2021.05.015>
- [10] Lin, Z., Zheng, J., Chen, M., Chen, J., & Lin, J. (2022). The Efficacy and Safety of Chinese Herbal Medicine in the Treatment of Knee Osteoarthritis: An Updated Systematic Review and Meta-Analysis of 56 Randomized Controlled Trials. *Oxidative medicine and cellular longevity*, 2022, 6887988. <https://doi.org/10.1155/2022/6887988>
- [11] Lao, L., Hochberg, M., Lee, D. Y. W., Gilpin, A. M. K., Fong, H. H. S., Langenberg, P., Chen, K., Li, E. K., Tam, L. S., & Berman, B. (2015). Huo-Luo-Xiao-Ling (HLXL)-Dan, a Traditional Chinese Medicine, for patients with osteoarthritis of the knee: a multi-site, randomized, double-blind, placebo-controlled phase II clinical trial. *Osteoarthritis and cartilage*, 23(12), 2102–2108. <https://doi.org/10.1016/j.joca.2015.06.007>
- [12] Maroon, J. C., Bost, J. W., & Maroon, A. (2010). Natural anti-inflammatory agents for pain relief. *Surgical neurology international*, 1, 80. <https://doi.org/10.4103/2152-7806.73804>
- [13] Pan, L., Zhou, J., Zhu, H., Wang, W., Zhang, M., Tian, X., Lu, J., & Zeng, M. (2014). Study on integrated pharmacokinetics of gardenia acid and geniposide: time-antioxidant efficacy after oral administration of Huanglian-Zhizi couplet medicine from Huang-Lian-Jie-Du-Tang in MCAO rats. *The American journal of Chinese medicine*, 42(2), 393–407. <https://doi.org/10.1142/S0192415X14500268>
- [14] Zhao, J., Huang, H., Liang, G., Zeng, L. F., Yang, W., & Liu, J. (2020). Effects and safety of the combination of platelet-rich plasma (PRP) and hyaluronic acid (HA) in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *BMC musculoskeletal disorders*, 21(1), 224. <https://doi.org/10.1186/s12891-020-03262-w>
- [15] Huang, Z., Mao, X., Chen, J., He, J., Shi, S., Gui, M., Gao, H., & Hong, Z. (2022). The Efficacy and Safety of Zhengqing Fengtongning for Knee Osteoarthritis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Evidence-based complementary and alternative medicine : eCAM*, 2022, 2768444. <https://doi.org/10.1155/2022/2768444>
- [16] Zhao, J., Yang, W., Liang, G., Luo, M., Pan, J., Liu, J., & Zeng, L. (2022). The efficacy and safety of Jinwu Gutong capsule in the treatment of knee osteoarthritis: A meta-analysis of randomized controlled trials. *Journal of ethnopharmacology*, 293, 115247. <https://doi.org/10.1016/j.jep.2022.115247>
- [17] Campbell, C. M., Mun, C. J., Hamilton, K. R., Bergeria, C. L., Huhn, A. S., Speed, T. J., Vandrey, R., & Dunn, K. E. (2023). Within-subject, double-blind, randomized, placebo-controlled evaluation of combining the cannabinoid dronabinol and the opioid hydromorphone in adults with chronic pain. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, 48(11), 1630–1638. <https://doi.org/10.1038/s41386-023-01597-1>
- [18] Mintarjo, J. A., Poerwanto, E., & Tedyanto, E. H. (2023). Current Non-surgical Management of Knee Osteoarthritis. *Cureus*, 15(6), e40966. <https://doi.org/10.7759/cureus.40966>
- [19] Zeng, F., Wang, K., Duan, H., Xu, X. T., Kuang, G. Y., & Lu, M. (2023). Diacerein versus non-steroidal anti-inflammatory drugs in the treatment of knee osteoarthritis: a meta-analysis. *Journal of orthopaedic surgery and research*, 18(1), 308. <https://doi.org/10.1186/s13018-023-03786-6>
- [20] Cowan, K. J., Kleinschmidt-Dörr, K., Gigout, A., Moreau, F., Kraines, J., Townsend, R., Dolgos, H., & DeMartino, J. (2020). Translational strategies in drug development for knee osteoarthritis. *Drug discovery today*, 25(6), 1054–1064. <https://doi.org/10.1016/j.drudis.2020.03.015>
- [21] Cao, P., Li, Y., Tang, Y., Ding, C., & Hunter, D. J. (2020). Pharmacotherapy for knee osteoarthritis: current and emerging therapies. *Expert Opinion on Pharmacotherapy*, 21(7), 797–809. <https://doi.org/10.1080/14656566.2020.1732924>
- [22] Gupta, S., Paliczak, A., & Delgado, D. (2021). Evidence-based indications of platelet-rich plasma therapy. *Expert review of hematology*, 14(1), 97–108. <https://doi.org/10.1080/17474086.2021.1860002>
- [23] Babalonis, S., Lofwall, M. R., Sloan, P. A., Nuzzo, P. A., Fanucchi, L. C., & Walsh, S. L. (2019). Cannabinoid modulation of opioid analgesia and subjective drug effects in healthy humans. *Psychopharmacology*, 236(11), 3341–3352. <https://doi.org/10.1007/s00213-019-05293-1>
- [24] Nielsen, S., Picco, L., Murnion, B., Winters, B., Matheson, J., Graham, M., Campbell, G., Parvaresh, L., Khor, K. E., Betz-Stablein, B., Farrell, M., Lintzeris, N., & Le Foll, B. (2022). Opioid-sparing effect of cannabinoids for analgesia: an updated systematic review and meta-analysis of preclinical and clinical studies. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, 47(7), 1315–1330. <https://doi.org/10.1038/s41386-022-01322-4>
- [25] Dobson, F., Hinman, R. S., Hall, M., Terwee, C. B., Roos, E. M., & Bennell, K. L. (2012). Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review. *Osteoarthritis and cartilage*, 20(12), 1548–1562. <https://doi.org/10.1016/j.joca.2012.08.015>
- [26] Martel-Pelletier, J., & Pelletier, J. P. (2010). Effects of diacerein at the molecular level in the osteoarthritis disease process. *Therapeutic advances in musculoskeletal disease*, 2(2), 95–104. <https://doi.org/10.1177/1759720X09359104>

- [27] Moldovan, F., Pelletier, J. P., Jolicoeur, F. C., Cloutier, J. M., & Martel-Pelletier, J. (2000). Diacerhein and rhein reduce the ICE-induced IL-1beta and IL-18 activation in human osteoarthritic cartilage. *Osteoarthritis and cartilage*, 8(3), 186–196. <https://doi.org/10.1053/joca.1999.0289>
- [28] Domagala, F., Martin, G., Bogdanowicz, P., Ficheux, H., & Pujol, J. P. (2006). Inhibition of interleukin-1beta-induced activation of MEK/ERK pathway and DNA binding of NF-kappaB and AP-1: potential mechanism for Diacerein effects in osteoarthritis. *Biorheology*, 43(3,4), 577–587.
- [29] Chen, B., Zhan, H., Marszalek, J., Chung, M., Lin, X., Zhang, M., Pang, J., & Wang, C. (2016). Traditional Chinese Medications for Knee Osteoarthritis Pain: A Meta-Analysis of Randomized Controlled Trials. *The American journal of Chinese medicine*, 44(4), 677–703. <https://doi.org/10.1142/S0192415X16500373>
- [30] Zhang, Y. S., Han, J. Y., Iqbal, O., & Liang, A. H. (2018). Research Advances and Prospects on Mechanism of Sinomenin on Histamine Release and the Binding to Histamine Receptors. *International journal of molecular sciences*, 20(1), 70. <https://doi.org/10.3390/ijms20010070>
- [31] Zhang, W., Wang, S., Zhang, R., Zhang, Y., Li, X., Lin, Y., & Wei, X. (2016). Evidence of Chinese herbal medicine Duhuo Jisheng decoction for knee osteoarthritis: a systematic review of randomised clinical trials. *BMJ open*, 6(1), e008973. <https://doi.org/10.1136/bmjopen-2015-008973>