

Rheumatoid Arthritis Treatments

Defining Arthritis

Arthritis is known as the inflammation or swelling of one or more joints in the body. It entails more than 100 different conditions that affect the joints, tissues around the joint, and other connective tissues. Specific symptoms vary depending on the type of arthritis, however, they all usually include joint pain and stiffness, which typically worsen with age. Arthritis impacts many more Canadians than most people realize. About 6 million Canadians (1 in 5 adults) have a certain type of arthritis, and its impacts usually extend to their family members, caregivers, and friends. In Canada, arthritis is more common in women than men (1 in 4 women, compared to 1 in 6 men) (Kasman et al. 2003). It can also affect people of any age. While it becomes more common at older ages, over half of Canadians suffering from arthritis are younger than the age of 65 (Badley et al. 2019).

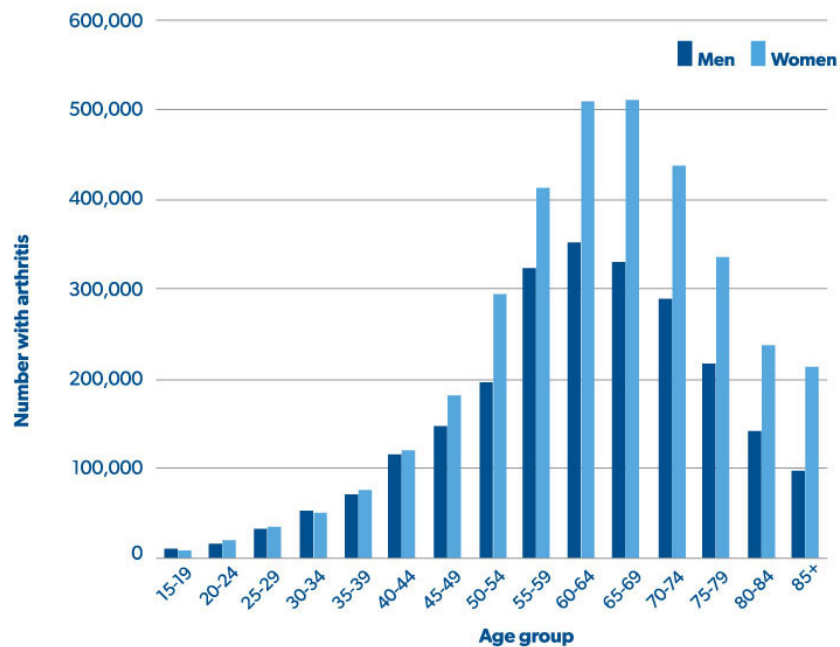


Fig 1. Distribution of the different ages and genders of Canadians suffering with arthritis (Arthritis Facts, Figures and Statistics | Arthritis Society Canada. Arthritis Society Canada. [accessed 2022 November 27]. <https://arthritis.ca/about-arthritis/what-is-arthritis/arthritis-facts-and-figures>).

Types of Arthritis

Osteoarthritis

There are many types of arthritis, including osteoarthritis (OA), rheumatoid arthritis (RA), fibromyalgia, and gout. Osteoarthritis (OA) is one of the most common types of arthritis. It can damage almost any joint but mainly occurs in the hands, spine, hips, and knees. Osteoarthritis was once considered a ‘wear-and-tear disease’ in which cartilage — the protective layer on the ends of bones — wore down after years of use and age (Rath 2019). But with further research, doctors now know that OA is a disease of the whole joint, not just the cartilage (Rath 2019). Bones in affected joints become weaker, the connective tissue that holds the joint together deteriorates, and inflammation damages the joint lining (Rath 2019). These changes usually develop slowly and get worse over time with age. OA can cause pain, stiffness, and swelling (CDC 2020). In some cases, it can also cause reduced function and disability; some people are no longer able to do daily chores or go to work (CDC 2020). OA can be effectively treated and managed with medication and self-management strategies. Currently, there is no cure for OA, so doctors usually treat OA symptoms with a combination of therapies, which may include increasing physical activity, physical therapy with muscle strengthening exercises, weight loss, medications (over-the-counter pain relievers and prescription drugs), supportive devices such as crutches or canes, and surgery if the other treatment options have not been effective (CDC 2020).

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune and inflammatory disease. This means that your immune system attacks healthy cells in your body by mistake, causing inflammation in the affected parts of the body. RA usually attacks many joints at once usually in the hands, wrists, and knees (CDC 2020). If a person is suffering from RA, in a joint, the lining becomes inflamed,

causing damage to joint tissue. This tissue damage can cause long-lasting or chronic pain, unsteadiness (lack of balance), and deformity (misshapeness) (CDC 2020). RA can also affect other tissues throughout the body and cause problems in organs such as the lungs, heart, and eyes (Mayo Clinic 2021). With RA, there are times when symptoms get worse, known as “flares”, and times when symptoms get better, known as “remission”. Some signs and symptoms of RA include pain or aching, stiffness, tenderness and swelling, weight loss, fever, fatigue or tiredness, and weakness (Mayo Clinic 2021). RA is diagnosed by examining symptoms, conducting a physical examination, and conducting X-rays and lab tests. RA can be effectively treated and managed with medication and self-management strategies, as well. Treatment for RA usually includes the use of medications that slow the spread of disease around the body and prevent joint deformity, called disease-modifying antirheumatic drugs (DMARDs); biological response modifiers are medications that are an effective second-line treatment (CDC 2020). However, there is no singular way to resolve RA.

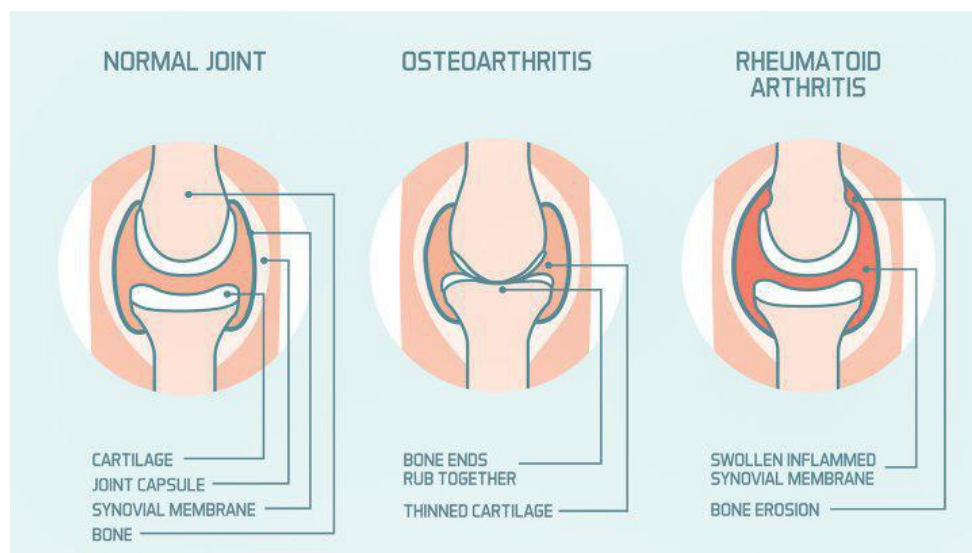


Fig 2. Picture showing the difference between OA and RA in joints (Nohr M. 2021. Joint Pain:

Top 12 Natural Strategies for Pain Relief. Dr. Jockers.com. Available from:

<https://drjockers.com/joint-pain-strategies-pain-relief/>).

Fibromyalgia

Fibromyalgia is a condition that causes pain all over the body (widespread pain), sleep problems, fatigue, and often emotional and mental distress (CDC 2020). People suffering from fibromyalgia are more sensitive to pain than those who are not; this is called abnormal pain perception processing. The most common symptoms of fibromyalgia are pain and stiffness all over the body, fatigue and tiredness, depression and anxiety, sleep problems, problems with thinking, memory, and concentration, headaches (including migraines), tingling or numbness in hands and feet, pain in the face or jaw (such as TMJ; temporomandibular joint syndrome), and digestive problems (ex: IBS; irritable bowel syndrome) (CDC 2020). People who have suffered from stressful or traumatic events (ex: car accidents), post-traumatic stress disorder (PTSD), and repetitive injuries are more likely to suffer from fibromyalgia (CDC 2020). Doctors usually diagnose fibromyalgia using the patient's history, physical and mental examination, X-rays, and blood work. Doctors usually treat fibromyalgia with a combination of treatments, which may include medications, aerobic exercise and muscle strengthening exercise, patient education classes, stress management techniques (ex: meditation, yoga, massage), good sleep habits, and cognitive behavioural therapy (CBT) to treat underlying depression (CDC 2020).

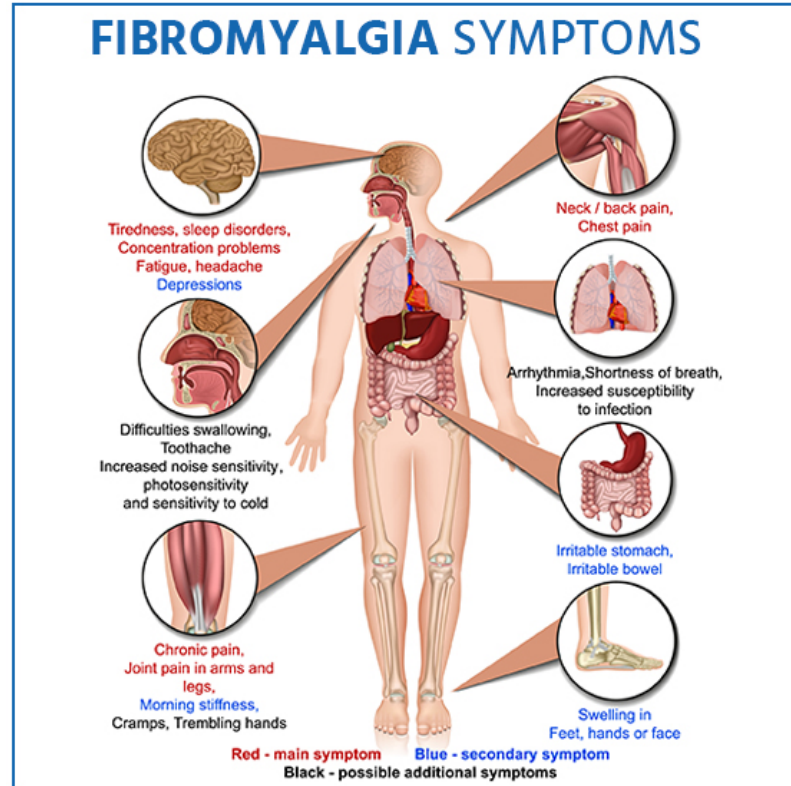


Fig 3. Picture describing the symptoms of fibromyalgia and where it affects the body (Rao KS. [Internet]. What is Fibromyalgia? Medicover Hospitals; [cited 2022 Nov 11]. Available from: <https://www.medicoverhospitals.in/diseases/fibromyalgia/>).

Gout

Lastly, gout is a common and complex form of arthritis that can affect anyone. It is characterized by sudden, severe attacks of pain, swelling, redness and tenderness in one or more joints, most often in the big toe (Mayo Clinic 2022). The affected joint is hot, swollen and so tender that even the weight of a bedsheet on it may seem intolerable. Gout occurs when urate crystals accumulate in your joint, causing the inflammation and intense pain of a gout attack (Weisman). Urate crystals can form when you have high levels of uric acid in your blood. Your body produces uric acid when it breaks down purines — substances that are found naturally in your body. Purines are also found in certain foods, such as red meat. Normally, uric acid dissolves in your blood and

passes through your kidneys and excreted into your urine. But sometimes either your body produces too much uric acid, or your kidneys excrete too little uric acid. When this happens, uric acid can build up, forming sharp, needle-like urate crystals in a joint or surrounding tissue that cause pain, inflammation, and swelling. Other symptoms include intense joint pain, lingering discomfort, inflammation and redness, and limited range of motion (Mayo Clinic 2022).

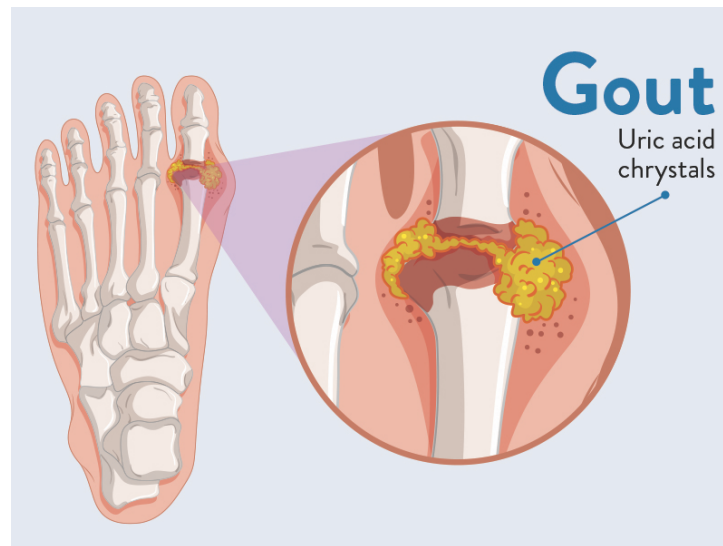


Fig 4. Picture describing how a gout attack (with uric acid crystals) would look on a big toe (Weisman S. About Gout: Managing and Preventing Attacks - Boulder Medical. Boulder Medical Center. [accessed 2022 November 27]. <https://www.bouldermedicalcenter.com/about-gout-causes-symptoms-and-treatment/>).

Treatments for Rheumatoid Arthritis

Rheumatoid arthritis (RA) is one of the most common inflammatory rheumatic diseases, affecting almost 1% of the world population (Magne et al. 2021). RA has a significant impact on the ability to perform daily activities including simple work and household chores. Nonetheless, due to the long periods of pain and the continuous use of anti-inflammatory drugs, RA can weaken the quality of life and increase mortality (Guo et al. 2018). Unfortunately, there is no

complete therapy for this disease, and the current treatments possess numerous side effects.

Thus, a novel therapeutic approach is necessary.

In the past three to five years, various research has been done to try and discover alternate therapies and treatments to help alleviate the symptoms of RA. Specifically, the use of silk fibroin hydrogel containing *Sesbania sesban* L. extract and hydroxychloroquine and methotrexate co-loaded nano micelles have been tested as rheumatoid arthritis treatments.

Novel Approach #1: Silk fibroin hydrogel containing *Sesbania sesban* L. extract

A study was developed in March 2022 where novel silk fibroin in-situ with a hydrogel containing *Sesbania sesban* L. extract (SS), a plant with high anti-inflammatory actions, was used against rheumatoid arthritis. According to Pham et al., the leaves and flowers of SS were collected in Phong Dien district, Can Tho, Vietnam, in April 2021. Fibroin, an insoluble protein present in silk produced by numerous insects, was extracted and purified from raw *Bombyx mori* silkworm cocoons (Pham et al. 2022). The fibroin was then turned into a powder and freeze-dried for future use. The freeze-dried fibroin powder was dissolved in de-ionized water at various concentrations. Then, the fibroin hydrogel was formulated. The hydrogels were manufactured using a simple method of spontaneous gelation at different temperatures. The gel properties of morphology, gelation time, viscosity, gel strength, stability, drug loading capacity, drug release rate, and in-vitro anti-inflammatory activity were investigated with appropriate methods (Pham et al. 2022). Then the SS was screened at various extraction conditions to find the optimal preparation with the highest total phenolic content (Pham et al. 2022). Phenolic compounds, one of the most diverse groups of plant secondary metabolites (ex: phenols, flavonoids, lignans, tannins, and cutins), have been demonstrated to help control the RA condition due to powerful anti-inflammatory properties (Shahidi et al. 2018). The in-vitro cumulative drug release profile of SSE (*Sesbania sesban* L.

extractions) loaded fibroin hydrogels, in terms of total polyphenol, was determined by the shaker method. The hydrogel was designed to be administered directly in the inflamed joint; thus, the drug release study was conducted in a simulated inflammatory joint condition (Pham et al. 2022). The best SS leaf extract was then encapsulated in the fibroin hydrogel, followed by gel characterizations (Pham et al. 2022). When the hydrogels were inserted in the simulated inflammatory joint condition, there was a constant release of the extract (with the phenolic content) for more than twenty days. This infers that these hydrogels can become a prospective rheumatoid arthritis treatment.

Novel Approach #2: Hydroxychloroquine and methotrexate co-loaded nano micelles

On the other hand, hydroxychloroquine and methotrexate co-loaded nano micelles have been tested as rheumatoid arthritis treatments. Nano micelles are one of the most widely used nanoparticles to improve the blood circulation time, bioavailability, and specificity of various therapeutic agents (Magne et al. 2021). Therapeutic agents can be selectively accumulated in the inflamed sites through passive or active targeting after systemic administration (Silvagni et al. 2019). In this way, the damage to other organs is remarkably reduced. The methodology described was that mice were immunized by subcutaneous injection on day 0 using methylated bovine serum albumin (mBSA). MBSA is used as a coating for immunoplates in enzyme-linked immunosorbent assay (ELISA). It has been widely used to induce antigen-specific inflammation in targeted organs or in combination with single-stranded DNA (ssDNA) to generate anti-nucleic acid antibodies in vivo. In this study, it is being used as a means to induce arthritis in mice models.

The mice were boosted with the same solution on day 7. Sham mice (fake immunized) received similar injections on day 0 and day 7, but without the antigen (mBSA) (Magne et al. 2021). On day 21, after the initial injection, arthritis was induced in the immunized animals by the

injection of mBSA. The sham mice received saline. From that period, the animals were treated daily, through intraperitoneal injections, for 7 days, and on the 25th day, a reinjection was performed using antigen (Magne et al. 2021). On day 28, mice were euthanized for further analysis. Therefore, in this study, the experimenters developed a novel hydroxychloroquine and methotrexate co-loaded nano micelle and evaluated its therapeutic effects against RA. Their results showed that drug-loaded nano micelles were capable of modulating the inflammatory process of RA and reducing osteoclastogenesis, edema, and cell migration to the joint, all of which are known symptoms of the body that attribute to arthritis. Interestingly, overall, compared to the free drugs, the drug-loaded nano micelles showed a 2-fold higher therapeutic effect.

Concluding Remarks

Arthritis is a serious disease that is disrupting the lives of many people around the world. More research must take place to be able to put an end to this disease. However, fortunately, both of these research experiments display the increase in attention to finding treatments for RA and how many different biological species can be used to do so. Either by releasing an extract that can manage bone collision or by inserting a certain antigen that can help the immune system to fight back against arthritis, both of these experiments show the light to the betterment of many people worldwide.

Paper #1: Silk fibroin hydrogel containing *Sesbania sesban* L. extract for rheumatoid arthritis treatment

<https://www.tandfonline.com/doi/pdf/10.1080/10717544.2022.2050848?needAccess=true>

Paper #2: Rheumatoid arthritis treatment using hydroxychloroquine and methotrexate co-loaded nanomicelles: In vivo results

<https://www.sciencedirect.com/science/article/pii/S0927776521003969?via%3Dihub>

References:

Badley EM, Wilfong JM, Zahid S, Perruccio AV. August 2019. The Status of Arthritis in Canada: National Report. Arthritis Community Research and Evaluation Unit (ACREU). Available from: https://arthritis.ca/getmedia/13aff08f-f206-4c6e-a709-beb80b97bd51/ACREU_Arthritis-Society_National-Report-2019_final.pdf

Centers for Disease Control and Prevention [Internet]. Jan 6, 2020. Fibromyalgia. Atlanta, GA; [cited: 2022 Nov 25]. Available from: <https://www.cdc.gov/arthritis/basics/fibromyalgia.htm>.

Centers for Disease Control and Prevention [Internet]. July 27, 2020. Osteoarthritis (OA). Atlanta, GA; [cited: 2022 Nov 25]. Available from: <https://www.cdc.gov/arthritis/basics/osteoarthritis.htm>.

Centers for Disease Control and Prevention [Internet]. July 27, 2020. Rheumatoid Arthritis (RA). Atlanta, GA; [cited: 2022 Nov 25]. Available from: <https://www.cdc.gov/arthritis/basics/rheumatoid-arthritis.html>.

Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. 2018. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Res*. National Library of Medicine [Internet]. [cited: 2022 Nov 25]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5920070/> doi: 10.1038/s41413-018-0016-9

Kasman NM, Badley EM. 2003. The impact of arthritis on Canadian women. *PsycEXTRA Dataset*. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2096689/>. DOI:10.1037/e615452012-018

Magne TM, Helal-Neto E, Correa LB, Alencar LMR, Piperni SG, Iram HI, Bhattarai P, Zhu L, Ricci-Junior E, Henriques M, Rosas EC, Santos-Oliveira R. Rheumatoid arthritis treatment using hydroxychloroquine and methotrexate co-loaded nanomicelles: In vivo results. [Internet]. [updated: 2021 June 11; cited: 2022 Nov 25]; Volume 206.111952. ISSN 0927-7765. Available from: <https://www.sciencedirect.com/science/article/pii/S0927776521003969> DOI: <https://doi.org/10.1016/j.colsurfb.2021.111952>.

Mayo Clinic. [Internet]. May 18, 2021. Florida (USA): Mayo Clinic. [cited 2022 Nov 25]. Available from: <https://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/symptoms-causes/syc-20353648>.

Mayo Clinic. [Internet]. Nov 16, 2022. Florida (USA): Mayo Clinic. [cited 2022 Nov 25]. Available from: <https://www.mayoclinic.org/diseases-conditions/gout/symptoms-causes/syc-20372897>.

Nohr M. 2021. Joint Pain: Top 12 Natural Strategies for Pain Relief. Dr. Jockers.com. Available from: <https://drjockers.com/joint-pain-strategies-pain-relief/>.

Pham DT, Thao NTP, Thuy BTP, De Tran V, Nguyen TQC, Nguyen NNT. [Internet]. (March 11 2022). Silk fibroin hydrogel containing *Sesbania sesban* L. extract for rheumatoid arthritis treatment, Drug Delivery, 29:1, 882-888. [cited: 2022 Nov 25]; Available from: <https://www.tandfonline.com/doi/pdf/10.1080/10717544.2022.2050848?needAccess=true> DOI: 10.1080/10717544.2022.2050848

Rao KS. [Internet]. What is Fibromyalgia? Medicover Hospitals; [cited 2022 Nov 25]. Available from: <https://www.medicoverhospitals.in/diseases/fibromyalgia/>.

Rath L. [Internet]. June 9, 2022. What is Arthritis? Atlanta (USA): Arthritis Foundation; [updated: June 9, 2022; cited 2022 Nov 25]. Available from: <https://www.arthritis.org/health-wellness/about-arthritis/understanding-arthritis/what-is-arthritis>

Shahidi F, Yeo J. [Internet]. (May 25 2018). Bioactivities of Phenolics by Focusing on Suppression of Chronic Diseases: A Review. [cited: 2022 Nov 25]; Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6032343/> DOI: 10.3390/ijms19061573
Silvagni E, Di Battista M, Bonifacio AF, Zucchi D, Governato G, Scirè CA. One year in review 2019: novelties in the treatment of rheumatoid arthritis. Clin Exp Rheumatol. 2019 Jul-Aug;37(4):519-534. Epub 2019 May 24. PMID: 31140394.

Weisman S. About Gout: Managing and Preventing Attacks - Boulder Medical. Boulder Medical Center. [accessed 2022 November 25]. <https://www.bouldermedicalcenter.com/about-gout-causes-symptoms-and-treatment/>.