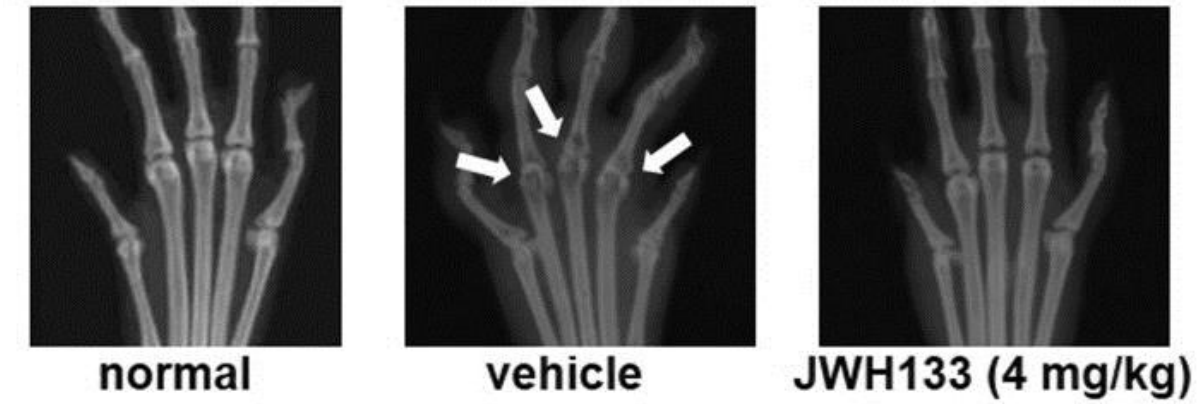
Basic Science of Medical Cannabis

Much of what is known about the mechanisms of action of bioactive cannabis chemicals (cannabinoids) is based on preclinical research in animals. Cannabinoids from plants (Phyto cannabinoids) and human cannabinoids (endocannabinoids) work through a primary series of receptors in the body, including CB1 receptors, which are found throughout the brain and central nervous system, and the CB2 receptors, which are found in the immune system, in bone, and in many organs including the heart, lungs, liver, GI tract, and spleen. This system of cannabinoid compounds and its receptors is known as the Endocannabinoid System.

Using synthesized chemicals that bind strongly to cannabinoid CB1 and CB2 receptors and to enzymes such as FAAH in animals, scientists can probe the effects of the Endocannabinoid System on certain common disease models such as rheumatoid arthritis, osteoporosis, and chronic pain.

In mice, the injection of collagen is known to induce rheumatoid arthritis-like condition (collagen-induced arthritis). In one study, scientists administered collagen to two groups of mice. In one group, the control (vehicle) group, there was nothing else given, and typical rheumatoid arthritis developed. In a second group, the mice were pretreated with a chemical that binds strongly to the CB2 receptor (JWH133). In this group, the development of rheumatoid arthritis was prevented[1]. This suggests a potentially important role of endocannabinoids in regulating the immune system.



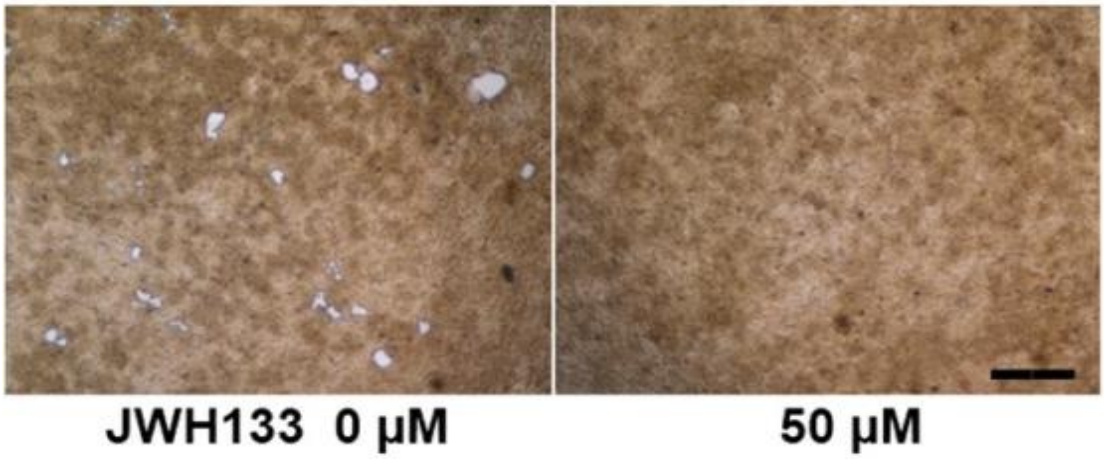
On the left is a normal mouse paw.

In the middle is a mouse paw after being given collagen (vehicle). Arrows show rheumatoid arthritis erosions.

On the right is a mouse paw after being given CB2 receptor stimulator JWH133 and then collagen. This paw looks normal.

Research has shown that CB2 receptors are present on the cells that regulate bone formation and breakdown (osteoblasts and osteoclasts). In another animal study, the CB2 receptor stimulator JWH133

was able to reverse osteoporosis in mice[2]. This suggests that endocannabinoids may play an important role in regulating human bone health.



On the left is osteoporotic mouse bone before JWH133 is given which shows typical "holes" in bone of osteoporosis. On the right is the same bone after JWH133 is given which shows that the holes in bone are gone and the bone is now stronger and denser.

The role of CB1 receptors has been studied in animal models. Rats with chronic pain have been found to produce more CB1 receptors in pain processing centers in the brain and stimulation of the CB1 receptors in mice has been shown to reduce responses to painful stimuli[3]. THC and the endocannabinoid anandamide have been shown to reduce tolerance to morphine and withdrawal symptoms from morphine in mice[4,5]. This suggests a possible role for cannabinoids in weaning humans from opioid medications.

Although these preclinical studies have produced impressive results in animal models of disease, it is important to acknowledge that they were performed using high doses of synthetic cannabinoid compounds and not with plant cannabinoids per se. Therefore, these results cannot be extrapolated to medical cannabis or to humans at this time. However, they do point towards future research possibilities and the prospect of pharmaceutical products that interact beneficially with the human endocannabinoid system.

1 Kinsey SG et al. **Fatty acid amide hydrolase blockade attenuates the development of collagen-induced arthritis and related thermal hyperalgesia in mice.** *Pharmacol Biochem Behav.* 2011 Oct; 99 (4): 718-725.

2 Bab et al**. Endocannabinoids and the regulation of bone metabolism**. *J. Neuroendocrinol.* 2008 May;20 Suppl 1:69-74.

3 Siegling A et al. **Cannabinoid CB(1) receptor upregulation in a rat model of chronic neuropathic pain**. *Eur J Pharmacol. 2001 Mar 9; 415(1):R5-7.*

4 Cichewicz, D.L. & Welch, S.P. 2003. **Modulation of oral morphine antinociceptive tolerance and naloxone-precipitated withdrawal signs by oral Delta 9-tetrahydrocannabinol.** *Journal of Pharmacology and Experimental Therapeutics* 305 (3): 812–17.

5 Vela G, et al. **Anandamide decreases naloxone-precipitated withdrawal signs in mice chronically treated with morphine.** *Neuropharamcology***.** 1995 Jun;34(6):665-8.