Cannabis: A plant with a potential worth investigating

Author: Reza Ghovaloo

Email: mghovanl@sfu.ca

Simon Fraser University

“Nothing will come of nothing.” This universal truth from Shakespeare’s play, King Lear, is an apt description of the need for cannabis research.

Much of the essence of research lies within a passion for debating. A healthy debate is often the foundation of formulating a hypothesis that seeks to answer a vital question. One of the most controversial topics for decades has been the use of cannabis. The controversy created a polarizing effect among researchers, policymakers, and the general public. On one side, there are extremists who see cannabis as a dangerous ‘weed’, a psychoactive drug that should be illegal. On the other extreme side, there are those who view cannabis as panacea, with the potential to treat every disease and condition known to man. The big question is simply, are there any merits to cannabis?

Cannabis originated in the Himalayas and was first cultivated in China for seed and fiber production (Elsohly, 2007). Early records of using cannabis medicinally can be traced to Sumerian records around 1800 B.C.E. (Friedman & Sirven, 2017), which mention using this plant against a variety of diseases (Russo et al., 2008), including convulsions. There are more recent records of cannabis use against epilepsy in Islamic literature (Nahas, 1982).

During the twentieth century, the use of cannabis became illegal in many parts of the world due to its psychoactive effects. These legal constraints made understanding the chemistry of cannabinoids elusive until the 1960s. Even after isolating some of the main cannabinoids, it took over twenty years to determine how one of the main cannabinoids, Δ9-tetrahydrocannabinol or THC, causes its well-known effects. THC led to identifying two cannabinoid receptors, CB1 and CB2. These receptors play many roles in our bodies, including pain response, mood, and memory, among others (Devane, Dysarz, Johnson, Melvin, & Howlett, 1988).

Although THC’s modulation of CB receptors could trigger the ‘high’ sensation, THC is reported to also be an analgesic, a muscle relaxant, and an anti-inflammatory agent. Because of its noteworthy side-effect, THC may not be an ideal therapeutic compound despite its potential benefits. Fortunately, there is another cannabinoid that has many of the same effects as THC without its psychoactive properties: cannabidiol (CBD).

Recently, several research groups have investigated some of the effects of CBD on various physiological systems. We now know that CBD has little to no affinity for the CB receptors with which THC interacts. So, CBD’s activity likely involves other receptor targets, including a group of proteins in charge of electrical signaling in the human body, known as voltage-gated ion channels. This has become a hot topic in ion channel basic research, as there are many conditions that are associated with the malfunctioning of various ion channels, such as Dravet syndrome (Ghovanloo et al., 2018; Kaplan, Stella, Catterall, & Westenbroek, 2017).

Dravet syndrome is a severe form of childhood epilepsy that is caused by loss of activity of a particular type of ion channels, known as sodium channels (subtype-1, Nav1.1), that ignite excitability in parts of the brain. The onset of this devastating condition typically occurs within the

first year of life, and upon onset, seizures become more frequent and unstoppable, in extreme cases, hundreds a week. This condition affects almost every aspect of development in children. The sheer frequency and intensity of these seizure attacks prevent the child from performing some of the most basic activities, including the ability to talk or walk. Unfortunately, each seizure also has the potential to be lethal (Dravet, 2011).

Luckily, a clinical trial published in 2017 reported CBD efficacy against Dravet Syndrome (Devinsky et al., 2017). However, there is still little known about the mechanism underlying this efficacy. To that end, my colleagues and I recently published a research paper leading to the discovery that CBD non-selectively reduces the activity of sodium channels (Ghovanloo et al., 2018).

Cannabis has also been suggested to have therapeutic effects in a range of other disorders. For instance, in patients with muscular dystrophy, cannabis could help to manage pain and involuntary muscle tightness. In patients that suffer from neuropathic pain, it could significantly reduce the intensity of chronic pain and also improve sleep. Cannabis also helps with involuntary muscle tightness and reduces muscle tremors and spasticity (Baker et al., 2000; Borgelt, Franson, Nussbaum, & Wang, 2013; Pertwee, 2008; Ware et al., 2010; Wilsey et al., 2013; Woodhams, Sagar, Burston, & Chapman, 2015).

In addition to THC and CBD, there are over a hundred cannabinoids and related compounds that can be isolated from cannabis. Our knowledge about most of these other cannabinoids is even more limited than THC and CBD. So, the next important question to ponder becomes, should we consider researching all of these cannabinoids?

The cannabis plant and its full range of compounds may or may not have any clinical merit. However, “nothing will come of nothing” until we put cannabinoids under the microscope of scientific research. And if there are therapeutic gems hidden in cannabis that can help the quality of life of some patients, then we should consider researching all of these cannabinoids. However, in the past, obtaining cannabinoids for research purposes required applying for an exemption from the Controlled Drugs and Substances Act, which could frequently take several months to process (Government of Canada, 2014). Still more hurdles are required if the cannabinoids are imported from outside Canada. Under the new system, cannabis researchers are required to apply for a licence under the Cannabis Tracking and Licensing System, which already warns of “several months” for processing (Health Canada, 2018).

This sounds like the same bureaucracy but with a different name. To put this in perspective, it took my colleagues and me 10 months to acquire 100 milligrams of CBD the first time we applied.

Indeed, progress in the cannabis research field would greatly benefit from a reduction in the bureaucratic process in obtaining cannabinoids. The downstream effect of these benefits could

be a more efficient discovery of compounds that, in turn, extend and enhance the lives of children who suffer from life-threatening conditions.

Bibliography

Baker, D., Pryce, G., Croxford, J. L., Brown, P., Pertwee, R. G., Huffman, J. W., & Layward, L. (2000). Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature*, *404*(6773), 84–87. https://doi.org/10.1038/35003583

Borgelt, L. M., Franson, K. L., Nussbaum, A. M., & Wang, G. S. (2013). The pharmacologic and clinical effects of medical cannabis. *Pharmacotherapy*, *33*(2), 195–209. https://doi.org/10.1002/phar.1187

Devane, W. A., Dysarz, F. A., Johnson, M. R., Melvin, L. S., & Howlett, A. C. (1988). Determination and characterization of a cannabinoid receptor in rat brain. *Molecular Pharmacology*, *34*(5), 605–613. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2848184

Devinsky, O., Cross, J. H., Laux, L., Marsh, E., Miller, I., Nabbout, R., … Cannabidiol in Dravet Syndrome Study Group. (2017). Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *The New England Journal of Medicine*, *376*(21), 2011–2020. https://doi.org/10.1056/NEJMoa1611618

Dravet, C. (2011). The core Dravet syndrome phenotype. *Epilepsia*, *52*, 3–9. https://doi.org/10.1111/j.1528-1167.2011.02994.x

Elsohly, M. A. (2007). *Marijuana and the Cannabinoids*. https://doi.org/10.1007/978-1-59259-947-9

Friedman, D., & Sirven, J. I. (2017, May). Historical perspective on the medical use of cannabis for epilepsy: Ancient times to the 1980s. *Epilepsy and Behavior*. https://doi.org/10.1016/j.yebeh.2016.11.033

Ghovanloo, M.-R., Shuart, N. G., Mezeyova, J., Dean, R. A., Ruben, P. C., & Goodchild, S. J. (2018). Inhibitory effects of cannabidiol on voltage-dependent sodium currents. *Journal of Biological Chemistry*, *293*(43), 16546–16558. https://doi.org/10.1074/jbc.RA118.004929

Government of Canada. (2014). Controlled Drugs and Substances Act. Retrieved February 11, 2019, from https://laws-lois.justice.gc.ca/eng/acts/C-38.8/page-13.html

Health Canada. (2018). *Cannabis Licensing Application Guide*. Retrieved from https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/industry-licensees-applicants/licensing-summary.html

Kaplan, J. S., Stella, N., Catterall, W. A., & Westenbroek, R. E. (2017). Cannabidiol attenuates seizures and social deficits in a mouse model of Dravet syndrome. *Proceedings of the National Academy of Sciences*, *114*(42), 11229–11234. https://doi.org/10.1073/pnas.1711351114

Nahas, G. G. (1982). Hashish in Islam 9th TO 18th Century. *Bulletin of the New York Academy*

of Medicine, *58*(9), 814–831. https://doi.org/10.1080/10848770.2013.791461

Pertwee, R. G. (2008). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *British Journal of Pharmacology*, *153*(2), 199–215. https://doi.org/10.1038/sj.bjp.0707442

Russo, E. B., Jiang, H. E., Li, X., Sutton, A., Carboni, A., Del Bianco, F., … Li, C. Sen. (2008). Phytochemical and genetic analyses of ancient cannabis from Central Asia. *Journal of Experimental Botany*, *59*(15), 4171–4182. https://doi.org/10.1093/jxb/ern260

Ware, M. A., Wang, T., Shapiro, S., Robinson, A., Ducruet, T., Huynh, T., … Collet, J. P. (2010). Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. *CMAJ*, *182*(14), E694-701. https://doi.org/10.1503/cmaj.091414

Wilsey, B., Marcotte, T., Deutsch, R., Gouaux, B., Sakai, S., & Donaghe, H. (2013). Low-dose vaporized cannabis significantly improves neuropathic pain. *Journal of Pain*, *14*(2), 136–148. https://doi.org/10.1016/j.jpain.2012.10.009

Woodhams, S. G., Sagar, D. R., Burston, J. J., & Chapman, V. (2015). The role of the endocannabinoid system in pain. *Handbook of Experimental Pharmacology*, *227*, 119–143. https://doi.org/10.1007/978-3-662-46450-2_7