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Editorial

Towards systematically assessing bioactivity of natural compounds or bio-ligands: Cannabidiol as an example

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Western medicine by law requires that drugs be synthetic compounds which are mass produced in heavily controlled manufacturing environments. In recent years there has been increasing interest in complementary and alternative medicine (CAM) for treating disease in the United States (e.g., White et al., 2017). Natural, non-vitamin, non-mineral dietary supplements account for a sizeable share of these approaches (17.7% in Clarke, Black, Stussman, Barnes, & Nahin, 2015). Despite their potential efficacy, a very small proportion of patients in the United States use CAM methods as complete replacements for standard pharmaceutical treatment (Nahin, Dahlhamer, & Stussman, 2010). Most CAM users reported taking natural dietary supplements for general wellness and preventative healthcare rather than specific outcomes (Marinac, Buchinger, Godfrey, Wooten, Sun, & Willsie, 2007). One reason is that identifying the dosages required for medicinal plant-derived compounds to treat specific diseases has proven difficult.

This was the case with cannabidiol (CBD). The CB2 receptor is a G-coupled protein receptor located predominantly in immune cells whose distribution and functions coincide closely with many observed immune effects of CBD (Ligresti, De Petrocellis, & Di Marzo, 2016). Despite hundreds of scientific articles written about CBD in recent times (Burstein, 2015; Zuardi, 2008), published displacement values (K_i) for the CBD/CB_2 interaction continue to vary substantially. Inconsistent results such as these make dosage recommendations impossible (Thomas, 2017). To solve this problem, a novel approach was developed to predict CBD/CB2 binding affinity between samples (Cushing, Kristipati, Shastri, and Joseph, 2018). Plant source and processing factors were identified to alter CB2 receptor affinity of CBD.

It is estimated that 75-78% of all modern medicines are directly or indirectly derived from higher plants (Samuelsson, 2004). Less than 5% of all plant species have been explored for their medical potential (Chin, Balunas, Chai, & Kinghorn, 2006). Natural plant compounds rarely have side effects. This makes them a potent alternative to pharmaceutical drugs for chronic use.

All active ingredients from plants are biological molecules. They have a complex biochemical pathway to produce a somatic effect on the human body. In order for plant materials to rival pharmaceutical drugs, they have to

undergo the same pharmaceutical factors – namely measurement of its bioactivity, knowledge of its pharmacokinetic and pharmacodynamic properties, and standardized quantities of active ingredient with the indential bioactive properties.

A three-step process for measuring bioactivity of all samples from natural plant-based sources will is outlined, using CBD as an example. This process is paramount for the application of natural plant-based compounds in western medicine.

3 steps for systematically assessing bioactivity:

The first step is to identify an important mechanism by which the compound studied acts on the body. In the case of CBD, decades of research have revealed multiple receptor targets. CB2 remains the most abundant cannabinoid receptor in the human body, and so it was the target of investigation by Cushing et al. (2018).

The second step is to develop a test that can compare the active compound from various samples. In most cases, direct tests of the mechanism of action are cumbersome. In these situations, scientists need to devise clever workarounds. CBD produces an indirect antagonistic effect on CB2 agonists WIN55212-2 and CP55290. In a binding assay, this antagonism can be measured using Chinese Hamster Ovary (CHO) cells with recombinant CB2 receptors. However, CHO membrane lines are expensive to generate, maintain, and test. So their use as a functional rapid tester for large quantities of CBD, over extended periods, is not practical. The experiment described in Cushing et al. utilized a Monoclonal Antibody (MCA) that displayed binding affinities to the CBD molecule with values that correlated highly (r = .97) to CB2 WIN55212-2 displacement values. This test was also simple to conduct. With such a high correlation, it became reasonable to predict CB2 affinity (and thus, bioactivity) with this more efficient MCA-based test.

The third step is to test samples for adequate bioactivity. In the case of CBD, Cushing et al. found that cannabis-based commercial samples had unanimously very low bioactivity compared to the ideal. This allowed them to issue a warning that standard commercial CBD samples should not be used for medical trials. Only tested products with high bioactivity should be used in medical studies.

To summarize, the three steps are as follows:

1) Identify the mechanism of action that relates to the bioactivity of the molecules.

2) Develop a test by which the bioactivity of the molecule can be measured.

3) Test commercial samples on a mass scale.

This three step process should be applied to all biological phyto compounds that have efficacy in the human body. Poor processing, pyrolysis, biodegradation, plant origin, and storage conditions can all affect the bioactivity of natural compounds. Research is undermined when it unwittingly uses low bioactivity samples. Knowing the bioactivity of an organic molecule is a key element in knowing its quality and functionality.

Conclusion:

It is estimated that 70-95% of the population in developing countries continues to use traditional medicines (Robinson & Zhang, 2011). Medical professionals in developed nations should account for natural plant ingredients as therapeutic agents. To this end, systematic control of factors that underlie variation in the bioactivity of natural plant compounds is paramount. A successful approach to testing the bioactivity of CBD between samples has been demonstrated. The same approach can be extended to natural medicinal compounds of all types. This extension has the potential to change the medical landscape globally, opening up a new frontier in western medicine.

References:

Burstein, S. (2015). Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. *Bioorganic & medicinal chemistry*, *23*(7), 1377-1385. https://doi.org/10.1016/j.bmc.2015.01.059

Chin, Y. W., Balunas, M. J., Chai, H. B., & Kinghorn, A. D. (2006). Drug discovery from natural sources. *The AAPS journal*, *8*(2), E239-E253. https://doi.org/10.1201/b11196-12

Clarke, T. C., Black, L. I., Stussman, B. J., Barnes, P. M., & Nahin, R. L. (2015). Trends in the use of complementary health approaches among adults: United States, 2002–2012. *National health statistics reports*, (79), 1.

Ligresti, A., De Petrocellis, L., & Di Marzo, V. (2016). From phytocannabinoids to cannabinoid receptors and endocannabinoids: pleiotropic physiological and pathological roles through complex pharmacology. *Physiological reviews*, *96*(4), 1593-1659. https://doi.org/10.1152/physrev.00002.2016

Marinac, J. S., Buchinger, C. L., Godfrey, L. A., Wooten, J. M., Sun, C., & Willsie, S. K. (2007). Herbal products and dietary supplements: a survey of use, attitudes, and knowledge among older adults. *The Journal of the American Osteopathic Association*, *107*(1), 13-23.

Nahin, R. L., Dahlhamer, J. M., & Stussman, B. J. (2010). Health need and the use of alternative medicine among adults who do not use conventional medicine. *BMC Health Services Research*, *10*(1), 220. https://doi.org/10.1186/1472-6963-10-220

Robinson, M. M., and Zhang, X (2011). The World Medicines Situation 2011. Traditional Medicines: Global Situation, Issues and Challenges, Geneya: World Health Organization.

Samuelsson, G. (ed.). (2004). *Drugs of Natural Origin: A Textbook of phamacognosy*, 5th Edn Stockholrn: Swedish Pharmaceutical Press.

Thomas, B. F. (2017). Cannabidiol as a Treatment for Seizures, Convulsions and Epilepsy. In *Cannabis sativa L.-Botany and Biotechnology* (pp. 249-261). Springer, Cham. https://doi.org/10.1007/978-3-319-54564-6_11

White, J. D., O'Keefe, B. R., Sharma, J., Javed, G., Nukala, V., Ganguly, A., ... & Walker, L. (2017). India-United States Dialogue on Traditional Medicine: Toward Collaborative Research and Generation of an Evidence Base. *Journal of Global Oncology*, JGO-17. https://doi.org/10.1200/jgo.17.00099

Zuardi, A. W. (2008). Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Revista brasileira de psiquiatria*, *30*(3), 271-280. https://doi.org/10.1590/s1516-44462008000300015