



## **Bioavailability of CBD Greatly Increased with VERUM's Nano-Enhanced CBD\***

**Introduction.** Cannabidiol (CBD) from industrial hemp is a multi-functional molecule. Scientific studies indicated that it may be a more powerful antioxidant than either Vitamin C or E, and CBD offers the prospect of successfully fighting chronic inflammation and protecting brain cells from reactive oxygen species (1-2).

CBD's beneficial potential is discussed in numerous published papers. It has promise in stabilizing and even reducing blood sugar levels; as a pain killer; for reducing the risk of artery blockage; in suppressing muscle spasms, seizures, and convulsions; for fighting varied cancers; and more (3-8).

Such promise is accompanied by a major limitation to its usefulness — low bioavailability. This means that any beneficial effects from CBD become patchy or erratic due to problems in getting CBD into the body in adequate amounts (9-14). For a supplement taken by mouth, bioavailability means the proportion of a dose that enters the bloodstream from the small intestine (15-17). Once in the blood, the supplement can find its way to the target organ or body system, where it then goes to work in supporting health and wellness.

On average, only 5-6% of almost any CBD preparation gets into the bloodstream. The rest is wasted. Such poor oral bioavailability guarantees variable or unpredictable effects, along with increased costs from having to take larger doses to compensate. Appropriate formulation strategies that assist in getting into the bloodstream are thus

mandatory for CBD to attain its health-giving potential, let alone in a cost-efficient or economical fashion.

**\*Manufactured for VERUM by Anano Technologies Inc.**

ANANDA Scientific (ANANDA) is VERUM CBD's product development and manufacturing partner. ANANDA'S research & development has yielded a patented CBD technology using GRAS ingredients that resolve CBD's bioavailability problem. This patented technology is the first of its kind. "GRAS" means that a substance is recognized as safe by the US Food and Drug Administration and that it can consequently be used in foods and beverages (18).

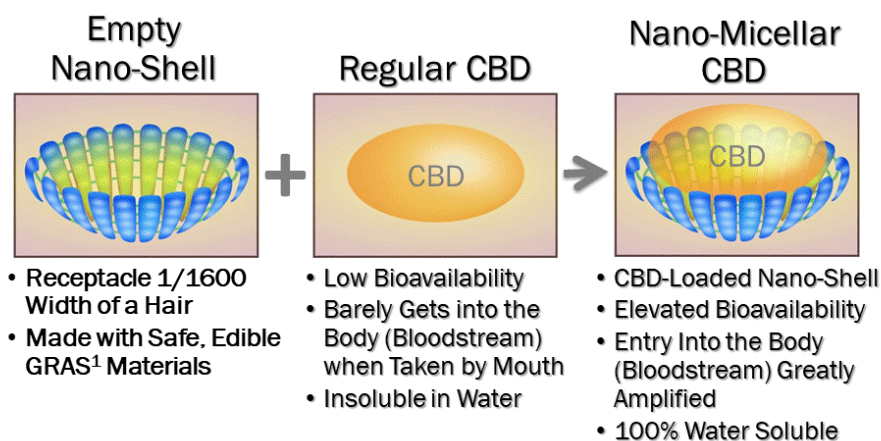


Figure 1. VERUM's patented, proprietary technology developed by ANADA SCIENTIFIC involves highly-ordered constructs made from GRAS compounds into which CBD is affixed. This technology makes nextCBD very bioavailable when taken by mouth.

**Purpose.** This study compares the bioavailabilities of regular CBD and VERUM'S enhanced CBD in laboratory rats. The bioavailability of substances taken by mouth are comparable between rats and humans (19-28).

**Methods.** This demonstration looks at the plasma contents of cannabidiol (CBD) after a single oral dose administered by gavage (through a tube leading down the throat to the stomach; 29) of regular CBD and VERUM'S enhanced CBD over a 24-hour period.

Female Sprague-Dawley rats (240-265 gm body weight) were used. The study design and animal usage were reviewed and approved by an Institutional Animal Care and Use Committee (IACUC) for compliance with regulations prior to study initiation. Animal welfare for this study with the U.S. Department of Agriculture's (USDA) Animal Welfare Act (9 CFR Parts 1, 2, and 3) and the Guide for the Care and Use of Laboratory Animals (30).

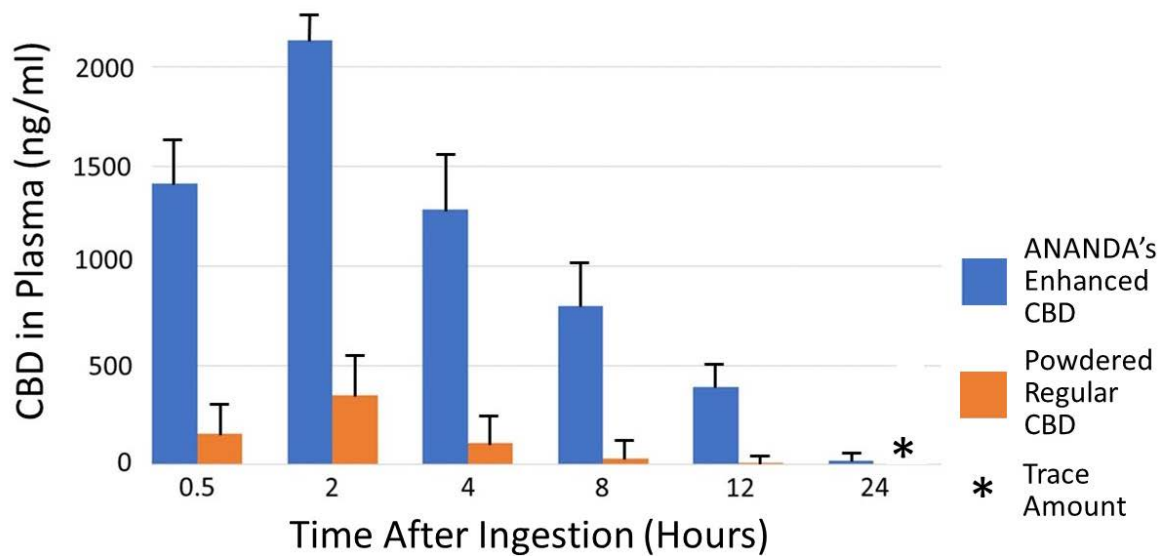
A 50-mg CBD/kg body weight model was examined in animals given VERUM'S nano-enhanced CBD and a control group for which powdered pure CBD in the same amount was fed. Ten animals were in each group.

Blood samples were taken immediately prior to gavage as well as 0.5, 1.0, 2.0, 4.0, 8.0, 12.0 and 24.0 hours after dosing. Venous blood was collected in an EDTA blood collection tube. Plasma was separated from red blood cells by centrifugation at 400g for 15

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quantified using validated high-performance liquid chromatography with tandem mass spectroscopy (LC-MS-MS) in multiple reaction monitoring (MRM) mode.

**Findings.** The results verify that VERUM'S enhanced CBD greatly improves bioavailability. It was tremendously more bioavailable than regular CBD at 0.5 and 2 hours. The results suggest far lower dosing is needed for enhanced CBD versus regular CBD. In other words, a little will go a long way. The results also intimate that products containing the regular, non-enhanced CBD found in most products may suffer from low bioavailability and a consequent ineffectiveness.



## References

1. Burstein, S. 2015. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. *Bioorganic & Medicinal Chemistry* 23(7):1377-1385.
2. Couch, D.G., H. Maudslay, B. Doleman, J.N. Lund, and S.E. O'Sullivan. 2018. The use of cannabinoids in colitis: a systematic review and meta-analysis. *Inflammatory Bowel Disease* 24(4):680-697.
3. Campos, A.C., M.V. Fogaça, A.B. Sonogo, and F.S. Guimarães. 2016. Cannabidiol, neuroprotection and neuropsychiatric disorders. *Pharmacological Research* 112:119-127.
4. Mannucci, C., M. Navarra, F. Calapai, E.V. Spagnolo, F.P. Busardò, R.D. Cas, F.M. Ippolito, G. Calapai. 2008. Neurological aspects of medical use of cannabidiol. *CNS & Neurological Disorders Drug Targets* 16(5):541-553.
5. McAllister, S.D., L. Soroceanu, and P.Y. Desprez. 2015. The antitumor activity of plant-derived non-psychoactive cannabinoids. *Journal of Neuroimmune Pharmacology* 10(2):255-267.
6. Pisanti, S., A.M. Malfitan, E. Ciaglia, A. Lamberti, R. Ranieri, G. Cuomo, M. Abate, G. Faggiana, M.C. Proto, D. Fiore, C. Laezza, and M. Bifulco. 2017. Cannabidiol: state of the art and new challenges for therapeutic applications. *Pharmacology & Therapeutics* 175:133-150.
7. Robson, P.J.: 2014. Therapeutic potential of cannabinoid medicines. *Drug Testing and Analysis* 6(1-2):24-30.
8. Russo, E.B. 2008. Cannabinoids in the management of difficult to treat pain. *Therapeutics and Clinical Risk Management* 4(1):245-259.
9. Agurell, S., S. Carlsson, J.E. Lindgren, A. Ohlsson, H. Gillspie, L. Hollister. 1981. Interaction of THC with cannabinol and cannabidiol following oral administration in man. Assay of cannabinol and cannabidiol by mass fragmentography. *Experientia* 37:1090-1092.
10. Gaston, T.E., and D. Friedman. Pharmacology of cannabinoids in the treatment of epilepsy. *Epilepsy & Behavior* 70(Pt. B):313-318.
11. , F. 2003. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clinical Pharmacokinetics* 42(4):327-360.
12. McGilveray, I.J. 2005. Pharmacokinetics of cannabinoids. *Pain Research and Management* 10(Suppl. A):15A-22A.
13. Ohisson, A., J.E. Lindgren, S. Andersson, S. Agurell, H. Gillespie, L.E. Hollister. 1986. Single-dose kinetics of deuterium-labeled cannabidiol in man after smoking and intravenous administration. *Biomed Environ Mass Spectrometry* 13:77-83.
14. Samara, E., M. Bialer, R. Mechoulam. 1988. Pharmacokinetics of cannabidiol in dogs. *Drug Metabolism and Disposition* 16:469-472.

15. Bhattaram, V.A., U. Graefe, C. Kohlert, and H. Derendorf. 2002. Pharmacokinetics and bioavailability of herbal medicinal products. *Phytomedicine* 9 (Suppl 3):1-33.
16. El-Kattan, A.F. 2017. *Oral Bioavailability Assessment: Basics and Strategies for Drug Discovery and Development (Wiley Series on Pharmaceutical Science and Biotechnology: Practices, Applications and Methods)*. First Edition. Wiley, New York, 448 p.
17. Hu, M., and X. Li. 2011. *Oral Bioavailability: Basic Principles, Advanced Concepts, and Applications*. First Edition. Wiley, New York, 568 p.
18. GRAS Substances (SCOGS) Database. U.S. Food and Drug Administration. <https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/SCOGS>
19. Akonur, A.I., C.J. Holmes, and J.k. Leypoldt. 2014. Predicting the peritoneal absorption of icodextrin in rats and humans including the effect of  $\beta$ -amylase activity in dialysate. *Peritoneal Dialysis International* 35(3):288-296.
20. Fagerholm, U., M. Johansson, and H. Lennernäs. 1996. Comparison Between Permeability Coefficients in Rat and Human Jejunum. *Pharmaceutical Research* 13(9):1336-1342.
21. Lawless E., B.T. Griffin B, A. O'Mahony A, and C.M. O'Driscoll. 2015. Exploring the impact of drug properties on the extent of intestinal lymphatic transport - in vitro and in vivo studies. *Pharmaceutical Research* 32(50):1817-1829.
22. Nagahara, N., Y. Akiyama, K. Higaki, and T. Kimura. 2006. Animal models for predicting potency of oral sustained-release adhesive microspheres in humans. *International Journal of Pharmacy* 331(1):46-53.
23. Pang, K.S. 2003. Modeling of intestinal drug absorption: roles of transporters and metabolic enzymes. *Drug Metabolism and Disposition* 31(12):1509-1517.
24. Salphati, L., K. Childers, L. Pan, K. Tsutsui, and L. Takahashi. 2001. Evaluation of a single-pass intestinal-perfusion method in rat for the prediction of absorption in man. *Journal of Pharmacy and Pharmacology* 53(7):1007-1013.
25. Stewart, B.H., O.H. Chan, R.H. Lu, E.L. Reyner, H.L. Schmid, H.W. Hamilton, B.A. Steinbaugh, and M.D. Taylor. 1995. Comparison of intestinal permeabilities determined in multiple in vitro and in situ models: relationship to absorption in humans. *Pharmaceutical Research* 12(5):693-699.
26. Zenghui Teng , Z., C. Yuan , F. Zhang, M. Huan, W. Cao, K. Li, J. Yang, D. Cao, S. Zhou, and Q. Mei. 2012. Intestinal absorption and first-pass metabolism of polyphenol compounds in rat and their transport dynamics in Caco-2 cells. *PLoS One* 7(1):e29647.
27. Zakeri-Milania,P., H. Valizadeha, H. Tajerzadehc, Y. Azarmia, Z. Islambolchilara, S. Barzegara, and M. Barzegar-Jalalia. 2007. Predicting human intestinal permeability using single-pass intestinal perfusion in rats. *International Journal of Pharmacy and Pharmaceutical Sciences* 10(3):368-379.

28. Zhang, D., and L\_X. Gang. 2012. Preclinical experimental models of drug metabolism and disposition in drug discovery and development. *Acta Pharmaceutica Sinica B* 2(6):549-561.
29. Andrews, K., and S. McErla. 2012. Oral dosing (gavage) in adult mice and rats. University of British Columbia Animal Care Guidelines, Standard Operating Procedure (SOP) ACC-2012-Tech09.
30. National Research Council and Division on Earth and Life Studies. 2011. *Guide for the Care and Use of Laboratory Animals*. Eighth Edition. National Academies Press, Washington, D.C., 246 p.