BECOMING AN EDUCATED CANNABINOID CONSUMER

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Summary

This article provides valuable information for making educated choices regarding the purchase of cannabinoid-containing products.

There are more and more oral and topical offerings in the cannabis space with claims of have high bioavailability, especially as it pertains to cannabidiol (CBD), meaning that a lot of what is taken reaches the bloodstream. Whether this is indeed the case is questionable when the proper information needed to verify is not available. Therefore, consumers need to carefully check out such products before making a purchase. To do this, only those bioavailability studies that employ proper scientific methods will prove reliable indicators of product legitimacy and dependability. In no uncertain terms, valid data to support claims of 100% bioavailability are a literal impossibility given the metabolic and physical obstacles to getting cannabinoids from the mouth or skin into the bloodstream. Cannabinoids then travel from the bloodstream to their sites of action, special receptors located on certain cells. Once there, different formulations with the same active ingredient can express unequal effects on performance.

Introduction

Cannabinoids, chemistry exclusive to cannabis plants (e.g., cannabidiol, tetrahydrocannabinol, cannibigerol, cannabichromene, cannabidivarin, tetrahydrocannabivarin), have progressed from illegal to legal status in more than half of the United States and in some countries. This is due more to political and social factors than scientific or medical ones, such as studies to more fully verify the therapeutic potential of cannabinoids. A bottom line is that there exists a lack of scientific work to confidently support health-related claims made about these molecules. This is due in no small way to obstacles placed by government on doing germane research. In addition, the methods of science do not come naturally to most people, and this is accompanied by a natural tendency to disregard what is difficult to understand. Ignorance and falsehood can then take precedence.
Pre-clinical studies and human clinical trials are especially striking by their absence. “Preclinical” refers to those studies that typically go before human clinical trials. It is from preclinical work that key parameters or attributes like bioavailability, dosing and safety are ascertained, and therapeutic targets identified.

It is undisputable that cannabinoids for fostering human health remains far from a matured, knowledge-rich discipline. Despite the public lack of scientific information needed for making cannabinoid-containing formulations that truly and reliably work, the manufacture and sales of commercial products have gotten underway. Whether these products are worth buying, or not, can be confusing for consumers.

For example, claims of substantial bioavailability, or how efficiently a substance is able to get into the bloodstream, are being made for many commercial offerings. As detailed below, greater bioavailability should be considered an essential product attribute. Difficulties in getting cannabinoids to there are considerable, and for a product to work as desired centers in no small way on how well a particular formulation reaches the bloodstream. Greater bioavailability means that more can get there.

Consumers must be diligent in differentiating between believable bioavailability claims predicated on real science and far-fetched ones based on mistaken or fraudulent premises. In that regard, the need for bona fide science cannot be understated. It provides information for being able to more confidently tell apart what really works and what does not.

It is herein contended that the bioavailability claims for certain products may be more due to ignorance and falsehood instead of facts. This article provides consumers with the background and perspective needed for making properly-informed product choices.

**What is Absolute Bioavailability?**

Absolute bioavailability refers to the fraction of a substance able to reach the bloodstream (where it can then be most readily transported to where it acts in the body) after having been introduced into the body – for example, as an injection, as pills and liquids taken by mouth or as a topical treatment. A bottom line is that determining bioavailability is essential for ensuring product safety, effectiveness and cost.

In essence, measuring absolute bioavailability entails comparing a formulation with a target substance against intravenous administration (IV; moving a substance into the bloodstream through a hypodermic syringe inserted into a
vein). Since all of a substance reaches the bloodstream with IV, it is deemed 100% bioavailable by definition.

Other delivery routes are associated with absolute bioavailabilities less than 100% due to multiple metabolic obstacles hindering entry into the bloodstream. Oral administration, i.e., taking a pill or a liquid, entails hurdles like breakdown in the stomach, difficulties in leaving the digestive system and destruction in the liver. These can prove huge barriers for getting necessary amounts of a substance into the bloodstream.

Nevertheless, oral and topical products are overwhelmingly preferred by consumers because of convenience and ease-of-use. But those involving an active ingredient with low bioavailability, as are cannabinoids, could prove functionally worthless and/or exceedingly costly. With absolute bioavailability improperly assessed, this circumstance becomes further problematic.

In no uncertain terms, bioavailability studies are the way to determine efficacy and safety, which makes it appropriate for consumers to request scrutiny of pertinent information in that regard before a purchase.

A product should be considered suspect or questionable without such evidence being made available.

The Need to Enhance the Absolute Bioavailability of Cannabinoids

A common rule in drug development is that, if oral bioavailability is very low, less than 20%, a substance should probably be excluded from commercial development. This is because of the unpredictable, irregular and lacking responses associated with low bioavailability, along with the use of costly and even hazardous amounts of a substance, to circumvent this problem. Whether as a pharmaceutical, functional food or dietary supplement, this should be a major topic of concern with cannabinoids because these have bioavailabilities of only 5-6% when taken by mouth.

For orally-consumed cannabinoids to become therapeutically worthwhile and economical, it consequently becomes important to employ technologies designed for safely getting more of a substance into the bloodstream. Being able to amplify cannabinoid bioavailability portends lessened dosages, which in turn make for reduced stress on the liver and other parts of the body along with cost savings to the consumer and a more predictable therapeutic response.

How is Bioavailability Examined?
Preclinical studies are the cornerstone for determining product attributes like absolute bioavailability, safety and toxicity. Such studies lead the way in providing necessary first answers about efficacy and safety for pharmaceuticals, nutraceuticals or functional foods, and dietary supplements.

Correctly prosecuting a bioavailability study is conceptually straightforward. In essence, it consists of some test subjects receiving a formulation of interest and others getting a preparation for comparison. For cannabinoids, formulations of interest may be those treated in a manner that is supposed to improve bioavailability. The comparison will be cannabinoids not subjected to any treatment.

Statistical analysis is employed to ensure that that perceived differences in a bioavailability study are meaningful and not due to chance. So, there needs to be enough subjects to ascertain statistical significance when there really exists a difference between the above-mentioned two groups.

A bioavailability study tends to be costly, and most often done with rats or mice. It usually does not go forward without surmounting another hurdle, demonstrating that subjects will be responsibly treated. A study, prior to getting underway, must be reviewed by a special committee to decide for or against an approval to go forward. The committee weighs the benefits of the study against possible or unavoidable injury and suffering. A scientifically-sound, well-designed bioavailability study will usually pass muster.

**Scrutinizing Bioavailability Studies**

Studies of absolute bioavailability studies must be done to make a credible claim, for which the following should be considered during consumer due diligence:

- Is there a written data summary, that justifies any bioavailability claims? If none exists, then the product in question should be deemed questionable or suspect.

- A written report will usually include a tabulation of the data along with a statistical analysis (briefly discussed below) of the study results. The report should ideally explain what was actually done in reasonable detail, i.e., the experimental design and sample preparation along with how or what statistics were applied.

- It is proper to inquire if bloodstream analyses were done at an analytical laboratory experienced in examining cannabinoids in bloodstream? In the United States, there are few facilities proficient in this regard. This
scarcity is due in no small way to legal prohibitions that have long plagued the cannabis industry.

- Bloodstream samples may be either serum or plasma as long the same sample type is used throughout. Serum is the liquid portion left after bloodstream clots. Plasma is generated from bloodstream treated with an anticoagulant (a substance that stops the clotting of bloodstream). Gravity causes red bloodstream cells to settle to the bottom. The straw-colored liquid on top is plasma.

- Statistical tests are the proper way to assess if differences between two different cannabinoid formulations have meaning (e.g., greater absolute bioavailability). Test results are not difficult to interpret. These are reported as probabilities or \( p \) values. As \( p \) values get lower (i.e., closer to 0% and farther away from 100%), it becomes more and more likely that a real difference exists. A \( p \) value of .05 is considered borderline, i.e., the cut-off for a bona fide difference. It means that there is a 95%, or 19 in 20, chance that differences in what are being compared are real. With a \( p \)-values of .001, the odds are 999 in 1,000.

- Bioavailability determinations help to ascertain how much cannabinoid should be administered to achieve a particular result. High bioavailability is associated with using lesser amounts of a target substance. The smaller the dose needed for efficiently getting a cannabinoid into the bloodstream, the more potent, predictable and cost effective will be the formulation.

**“100% Bioavailability” Is Not Real**

An unarguable premise is that oral and topical product offerings claiming “100% bioavailability” are not only a sham but also an impossibility, as above discussed. First, only IV administration involves no target substance loss. Second, the other ways for getting cannabinoids into the body involve some sort of degradation and other metabolic obstacles. Compared with the amount consumed or applied, less always reaches the bloodstream. A **bottom line is that claims of “100% bioavailability” for oral or topical products are predicated on mistaken, ignorant and even fraudulent premises, for which valid supporting data will always prove nonexistent.**

**Bioavailability -- Hemp versus Marijuana**

Some purport that marijuana trumps hemp in terms of bioavailability.
Marijuana and hemp come from the same plant, *Cannabis sativa*. Each typically has CBD but differs by levels of the psychoactive cannabinoid, tetrahydrocannabinol or THC. Hemp is *C. sativa* with 0.3% or less by law in dried plant material, an amount too low to get anyone “high”. In contrast, marijuana has 25% and sometimes more.

In any case, cannabinoid molecular structures are the same regardless of whether they come from hemp or marijuana. A bottom line for a purified cannabinoid is that there are no differences in performance irrespective of origin.

There are numerous genetic strains of both hemp and marijuana, and their chemical contents tremendously differ. Indeed, each contains not only cannabinoids but also a myriad of terpenes, phytosterols, alkaloids, flavonoids and more than 1,500 additional plant-derived substances.

As a consequence, tremendous differences in bioavailability inherently exist among the many cannabinoid products that have been extracted and concentrated (most often with supercritical carbon dioxide) but not purified.

Even with the same plant strain, circumstances become further complicated by differences in growing conditions from one place to another. These result in plants with dissimilar chemical compositions, and thus divergent bioavailabilities.

**True Bioavailability: Beyond the Bloodstream**

Efficiently reaching the bloodstream might be an initial indicator of product performance, but the buck stops at **true bioavailability** or **performance**, the degree to which a substance impacts its target. For cannabinoids, the target is not just the bloodstream and instead select locations within the body, specifically, **receptors on the outer surfaces of special cells**:

1. A certain receptor binds only with a particular substance, e.g., a cannabinoid like cannabidiol, tetrahydrocannabinol or cannabigerol. This binding initiates specific chemical responses inside the cell that may have profound consequences to health.

2. Most cannabinoids attach to “endocannabinoid” receptors CB1 and CB2, in the brain, spinal cord, spleen, immune system, endocrine glands (those glands that make hormones to regulate growth and development, sexual function, sleep, mood and more), reproductive system, intestines and urinary tracts.
3. Cannabidiol exceptionally does not, and instead has its own receptors. These are important for alleviating pain and reducing inflammation. CBD attaching to one receptor, GPR55, may be the foundation for a successful obesity therapy.

4. Besides the profound effects associated with cannabidiol’s receptors, this substance also has an indirect impact on the CB1 receptor – by helping promote the buildup of anandamide. Made in the body, anandamide binds to and is the primary regulator of the CB1 receptor. Higher levels of anandamide can desirably impact memory, motivation, speech and more.

**Importantly, it is important to recognize that different formulations containing the same active ingredient, once in the bloodstream, can have unequal true bioavailability.** Some will yield more desirable responses than others. How consumers should evaluate this phenomenon is a matter for future discussion.

**About Dr. Rosenfeld**

Dr. Rosenfeld has centered his professional attention on making cannabinoids acceptable human medicine for several years. He conceived and has directed the successful development of unique nanotechnologies to resolve unmet needs that have barred cannabinoids from widespread use to benefit human health.

Dr. Rosenfeld assisted the States of Kentucky, Pennsylvania and Utah in creating legislation for using cannabinoids for both medicine and functional foods. Formerly a Member of the Faculty at the University of Utah School of Medicine and a Scientific -- Medical Consultant to the United States House of Representatives, the China Ministry of Health and the United Nations, he holds 15 patents in pharmacology and molecular disease detection.

**About ANANDA Scientific, Inc.**

ANANDA Scientific’s activities are centered on developing effective products based on cannabis plant chemistry, to treat debilitating and even life-threatening health conditions impacting millions of people worldwide as well as for improving health in general. The Company is taking a science-based approach, for which it has advantageously positioned research, development and production. The Company’s R&D is situated largely in Israel, the global center for cannabis-related research, with product production done in the United States. ANANDA Scientific is also distinctively ensconced in China, where cannabinoid therapies could go far in helping resolve a huge public
health crisis there. Refer to ANANDA Scientific’s website for more information: www.anandascientific.com.