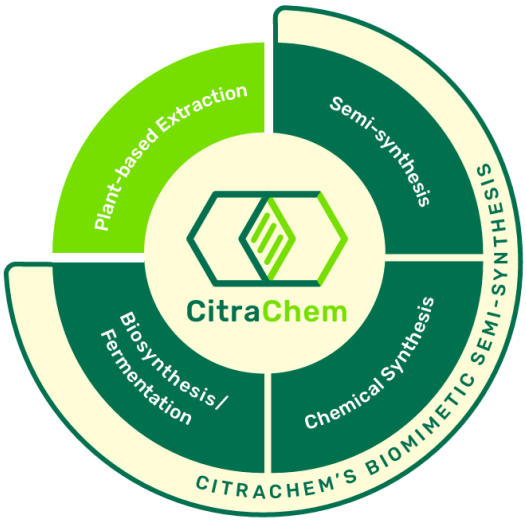
Mother Nature:
The Premier Molecular Architect

The Inspiration that led to CitraChem's Biomimetic Semi-synthesis Platform



A White Paper

November 15, 2024

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Introduction

Since the beginning of the regulated cannabis market in the United States, many have theorized about how the industry would evolve. Early on, there was foreshadowing of a future trifurcation in the industry; *i.e.*, the market would end up segmented among (1) those interested in using cannabis products casually (recreationally), (2) those focused on the effects of using cannabis in a self-directed or physician-guided manner to reduce their ailments or improve their health, and (3) those who prefer a highly endorsed medical product – a drug that has passed clinical trials and is prescribed by a doctor through the common channels.

That trifurcation is now upon us.

The goal of this white paper is to underscore CitraChem's point of view that cannabinoids derived from a biomimetic entry will aid in the development of new plant-based products and medicines. We do not intend to supplant one's ability to use botanical ingredients in any manner they choose. We shouldn't group humans as either "plant people" or "science people". Rather, we aim to ensure that everyone – from the casual consumer to medical patients – has safe and affordable access to the highest purity medicinal agents produced in ways that are environmentally sustainable.

Through this paper, we survey the history of drugs that were developed based on natural products, making a firm case that discovering new ways to utilize the metabolites plants produce for their own self-defense and communication has benefitted mankind repeatedly. In addition, we support the idea that CitraChem's general synthesis platform, that replicates nature's biochemistry in the plant, can accelerate research and development for phytochemicals by providing sources that are both ultra-pure and readily available.

As has been true for nearly every other market in traditional healthcare, there is a broad and dynamic spectrum of end users and medicinal applications – from those who want to consume the plant directly to those who prefer some baseline level of processing and carefully controlled dosing to target a specific physiological outcome.

The world can have it all. This is why we still have home remedies (like chicken soup), over-the-counter medications (like "ABC Severe Cold & Flu") and state-of-the-art pharmaceuticals (like the prescription antiviral Oseltamivir, aka Tamiflu).

Come along for a short journey, and after reading our point of view, we'd love your feedback. Please feel free to write to us.

Sincerely,

James Winokur, CEO, jwinokur@citrachem.com
Dr. Jason Kingsbury, Co-founder & CSO, jkingsbury@ctirachem.com

Chapter 1: Synthesis in Nature

How do plants form cannabinoid molecules?

To better appreciate why a biomimetic semi-synthesis approach is important to CitraChem, insight below provides a baseline understanding of plant biosynthesis.

Definitions *from Merriam-Webster's Dictionary*

Phytochemical
a chemical compound occurring naturally in plants

Synthetic
of, relating to, or produced by chemical or biochemical synthesis

Biosynthesis
the production of a chemical compound by a living organism

Synthesis
the production of a substance by the union of chemical elements, groups, or simpler compounds or by the degradation of a complex compound

Semi-synthetic
produced by chemical alteration of a natural starting material

Cannabinoids are primarily synthesized in the glandular trichomes of cannabis plants. Trichomes are small, hair-like structures found on the surface of the plant which are especially prevalent on the flowers of female plants. There are three main types of trichomes involved in phytocannabinoid production:

- Bulbous trichomes
- Sessile trichomes
- Stalked trichomes

The sessile and stalked trichomes are responsible for the majority of cannabinoid biosynthesis, an enzymatically controlled sequence that involves several steps:

Precursor Formation: The process begins with the metabolic buildup of two key building blocks (Figure 1):

- Olivetolic acid (derived from fatty acid metabolism)
- Geranyl pyrophosphate (GPP) (derived from the terpene pathway)

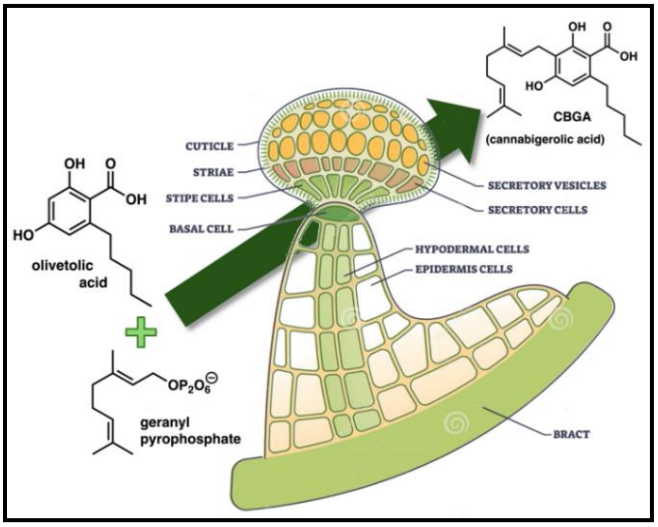

Figure 1

1. **CBGA Synthesis**: The precursors above are united by the enzyme geranylpyrophosphate-olivetolate geranyltransferase (GOT) to form cannabigerolic acid (CBGA), which is the central forerunner to all higher phytocannabinoids (Figure 2).

2. **Enzymatic Cyclization**: CBGA is then converted into cannabinoid acids through the action of shape-specific enzymes noted below. These enzymes are protein catalysts that vary in degrees of complexity associated with the molecular changes that they bring about:

    - CBCA synthase produces cannabichromenic acid (CBCA)
    - CBDA synthase produces cannabidiolic acid (CBDA)
    - THCA synthase produces tetrahydrocannabinolic acid (THCA)

2. **Decarboxylation**: Acid forms of cannabinoids undergo conversion to their neutral forms (e.g., CBC, CBD, THC) through a loss of carbon dioxide gas. This decarboxylation occurs naturally over time or can be accelerated under the influence of light and/or heat. As a practical example, the high temperature required to combust raw cannabis flower (when smoking) is well-known to convert both THCA and CBDA quantitatively into their neutral forms. Therefore, decarboxylation is not an aspect of the biosynthesis that the plants are genetically predisposed to. Nonetheless, it is commonplace and rather difficult to prevent once a cannabis plant has reached maturity.

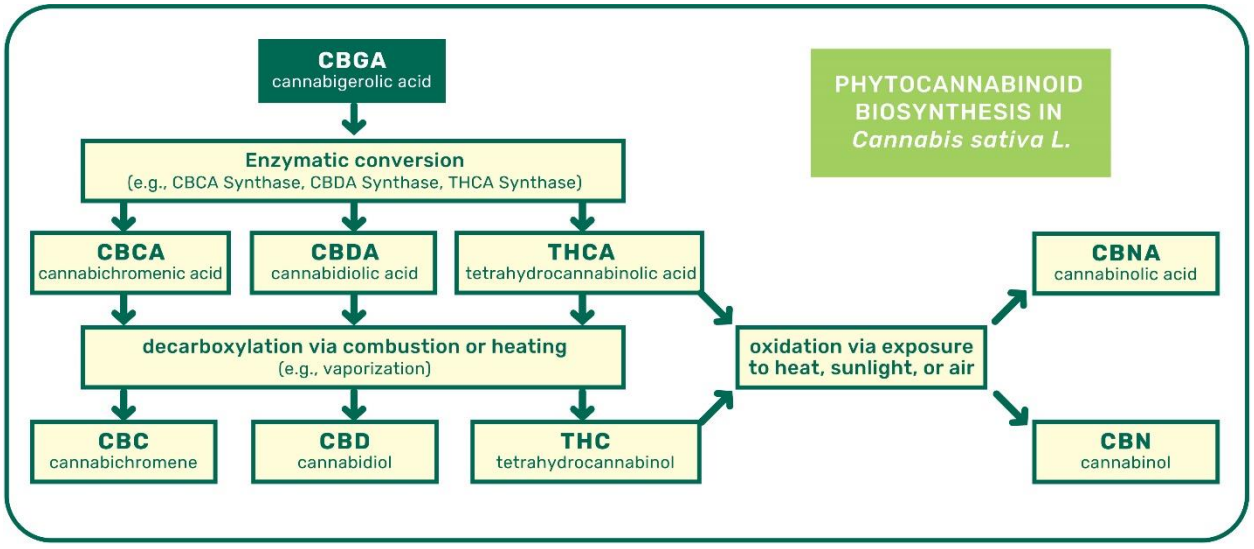

Figure 2

Chapter 2: Not Always 100% Natural

> *"I did not invent penicillin. Nature did that. I only discovered it by accident."*
>
> - Alexander Fleming

Sometimes scientific discoveries involve taking a natural active ingredient and figuring out how to increase its usefulness, administering it to humans after finding a suitable delivery mechanism, formulation and optimal dose. Frequently, a natural compound may not be available abundantly in Nature, so we are obligated to find ways to obtain the ingredient in volume while protecting the sanctity and integrity of the natural source.

The following describes the four main tactics used to source cannabinoid ingredients:

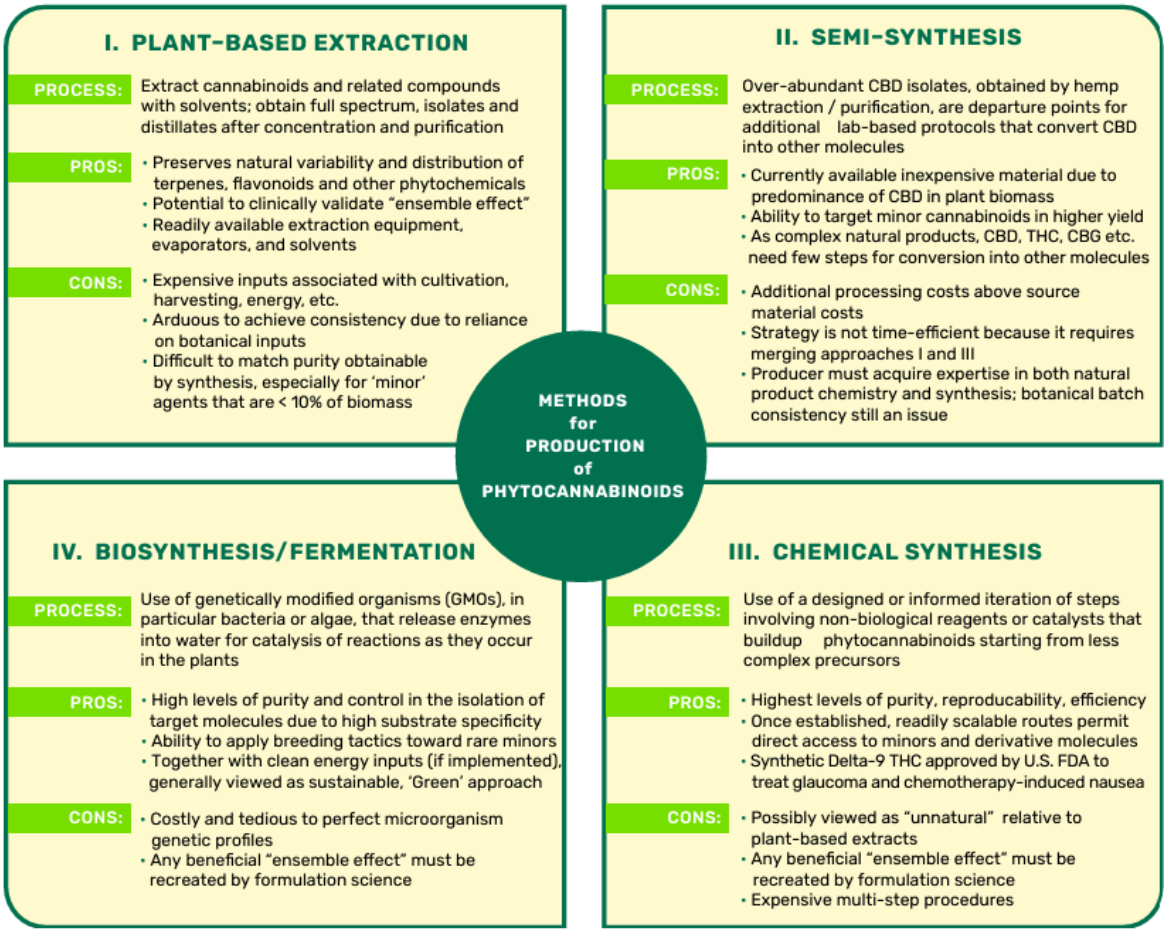

Figure 3

Each of these strategies has its pros and cons. CitraChem's unique biomimetic approach borrows processes from three of the four methods. Our strategy is not to extract cannabis or hemp biomass and tediously purify the resulting isolates. Instead, we begin with other plant-based terpenes, such as citral or (*R*)-limonene, relying upon the techniques of traditional organic and semi-synthesis and reactivities marked by the mild, catalytic conditions associated with plant enzymes. While utilizing

reagents in a lab, CitraChem's novel protocols align with the same logic as the plant because it is a powerhouse chemical factory honed over millions of years of evolution. The end result is a molecule that is exactly the same as what the plant produces but derived differently. Regardless of its origin, a molecule is a molecule.

Here are some examples of where Nature and science have met.

I. Plant-based extraction example

Epidiolex represents a significant advancement in epilepsy treatment, offering a pharmaceutical-grade CBD option for patients with specific seizure disorders. It is a prescription medication with the following key characteristics:

- Active ingredient: Epidiolex is an oral solution of cannabidiol (CBD) in purified form. CBD is the predominant chemical found in industrial strains of hemp.[1, 2]
- FDA approval: It is the first and only FDA-approved prescription CBD medication. [1]
- The drug is formulated as a 100 mg/mL solution in sesame oil as the primary vehicle with dehydrated alcohol, strawberry flavoring, and sucralose excipients.
- Indications: Epidiolex is approved to treat seizures associated with Lennox-Gastaut syndrome, Dravet syndrome and Tuberous sclerosis complex[1, 2]

While the active ingredient is extracted from a plant, it is initially processed as a chemical mixture, then rigorously purified, and subsequently blended with other elements for safe and effective delivery to humans. The process of FDA approval required clinical trials that led to a specific twice daily dosage. A flavor additive was incorporated because it is administered primarily to children over the age of 1.

[1] Epidiolex Website, https://www.epidiolex.com/

[2] *Medical News Today* Website, https://www.medicalnewstoday.com/articles/epidiolex

II. Semi-synthesis example

Taxol, also known by its generic name paclitaxel, has a fascinating origin story. The natural product is notable in having an exceedingly complex chemical structure, and its discovery ushered in the development of one of the most lifesaving and widely adopted cancer drugs in modern medicine.

Eventually, scientists were able to shorten the number of synthetic steps needed to manufacture the target by starting with the baccatin precursor abundant in the shrub-like European yew. The power of semi-synthesis thus lies in our ability to deliberately select other, typically more abundant plant-derived molecules as points of departure for industrial scale-up.

- Taxol was originally isolated from the bark of the Pacific yew tree (*Taxus brevifolia*) in 1967.[1, 2] The recovery was made as part of a large-scale plant screening program conducted by the National Cancer Institute (NCI) and the U.S. Department of Agriculture (USDA) between 1960 and 1981.[4]
- Initial samples were collected by USDA botanist Arthur Barclay in 1962 during an expedition in Washington State.[4, 5]
- In 1967, researchers Monroe E. Wall and Mansukh C. Wani at the Research Triangle Institute in North Carolina isolated and identified the active compound in the bark samples on the basis of its pronounced cytotoxic effects.[1, 4]
- Initially, Taxol was in critically short supply because it had to be extracted from the bark of the Pacific yew. Due to low natural abundance, it would take an entire 100-year-old yew tree to furnish a single patient dose of anti-cancer agent. Trees were harvested to near extinction in order to get sufficient quantities of Taxol for human clinical trials. [1, 3]
- The **supply problem was definitively solved through semi-synthetic production** methods, because a sufficiently complex precursor (10-deacetyl baccatin-III) was found in the needles of the more common European yew (*Taxus baccata*).[1, 6] This alternative natural source could be farmed and propagated more quickly, and the baccatin precursor could be isolated without sacrificing the entire plant.
- Taxol was approved by the FDA for medical use in 1992, initially for the treatment of breast and ovarian cancers.[2, 6]

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[1] Goodman, Jordan and Walsh, Vivien, 2001, Nature Medicine, *The Story of Taxol: Nature and Politics in the Pursuit of an Anti-Cancer Drug,* Cambridge University Press

[2] Wikipedia, Paclitaxel, https://en.wikipedia.org/wiki/Paclitaxel

[3] Cordes, Eugene, 2020, The discovery of Taxol: Wall, Horwitz, Holton, Oxford Academic, https://academic.oup.com/book/41768/chapter-abstract/354382165?redirectedFrom=fulltext

[4] Weaver, Beth A., 2014, How Taxol/paclitaxel kills cancer cells, The American Society of Cell Biology, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4161504/

[5] NIH: National Cancer Institute Website, A Story of Discovery: Natural Compound Helps Treat Breast and Ovarian Cancers https://www.cancer.gov/research/progress/discovery/taxol

[6] Ginsberg, Judah, 2003, The Discovery of Campthothecin and Taxol, American Chemical Society Office of Communications, https://www.acs.org/education/whatischemistry/landmarks/camptothecintaxol.html

III. Chemical synthesis example

The use of salicylates, the natural precursors to aspirin, dates back over 3,500 years. Ancient Sumerians and Egyptians used willow bark as a painkiller and antipyretic.[2] Greek physician Hippocrates (460-377 BCE) recommended willow leaves and bark to relieve pain and fever.[4]
In the 18th and 19th centuries, scientists began to investigate salicylic acid as a biologically active natural product:

- In 1763, Reverend Edward Stone conducted the very first clinical trial on record, applying willow bark in the treatment of malarial symptoms.[1]
- French pharmacist Henri Leroux isolated salicylic acid in 1829.[4]
- Hermann Kolbe replicated natural salicylic acid by chemical synthesis in 1874.[4]

The modern form of aspirin was developed in the late 19th century as a "pro-drug" strategy. On August 10, 1897, Felix Hoffmann, a chemist at Bayer, successfully synthesized pure acetylsalicylic acid (ASA) by acetylating the phenol group of salicylic acid.[1, 3] The results:

- ASA proved to be less harsh on the gastrointestinal system, and once absorbed into the bloodstream, it de-acetylates *in vivo*, giving the original willow bark ingredient to combat pain and fever with diminished side effects.
- Professor Heinrich Dreser, Head of Pharmacology at Bayer, tested the compound on himself and then in animal and human clinical trials.[3]
- In 1971, Sir John Vane unraveled aspirin's mechanism of action involving inhibition of prostaglandin synthesis, for which he later received the Nobel Prize in Medicine.[1, 3]
- In 1976, the enzyme cyclooxygenase (COX), aspirin's target, was successfully isolated.[1]

While the genesis of aspirin was a molecule found in nature, salicylic acid, it took creativity and research by chemists to produce an even more effective active ingredient. Traditional, start-to-finish chemical synthesis enabled rapid testing and screening of new derivatives, and ASA could be procured in quantity at low cost to advance a new medicine for the masses. The real magic of organic synthesis lies in its ability to forge matter anew, refining and improving upon Nature's spectacular starting points.[4]

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[1] Fuster, Valentin, MD, PhD, and Sweeny, Joseph M. MD, 2011, Aspirin: A Historical and Contemporary Therapeutic Overview, https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.110.963843

[2] Montinari, Maria Rosa, Minelli, Sergio, De Caterina, Raffaele, 2019, The first 3500 years of aspirin history from its roots - A concise summary, Science Direct, https://www.sciencedirect.com/science/article/abs/pii/S1537189118303549?via%3Dihub

[3] International Aspirin Foundation website, The story of Aspirin – a versatile medicine with a long history https://www.aspirin-foundation.com/history/the-aspirin-story/

[4] Landau, Elizabeth, 2010, From a tree, a 'miracle' called aspirin, CNN.com https://edition.cnn.com/2010/HEALTH/12/22/aspirin.history/index.html

IV. Biosynthesis/Fermentation example

The most well-known drug produced through fermentation is penicillin. The path from an unwanted mold contaminating a petri dish to a brand new, first-in-class protein inhibitor ushered in one of the most important advancements in healthcare: antibiotics.

Here are some key points regarding penicillin production *via* fermentation:

- Penicillin was discovered serendipitously by Alexander Fleming in 1928, ushering in the era of antibiotics.[1]
- At first, Fleming was unable to isolate penicillin in sufficient quantities, and he believed it would not remain in the body long enough to be effective.[2, 3]
- In 1940, a team at Oxford University led by Howard Florey and Ernst Chain began researching penicillin's potential as a therapeutic agent owing to its potent ability to disrupt bacterial cell wall biosynthesis.[2, 3]
- The latter researchers were able to produce penicillin in larger quantities and demonstrate its effectiveness.[3]
- In the early 1940s, scientists worked on increasing penicillin output using fermentation techniques, which are uniquely effective for beta-lactam structures.[4]
- Pfizer pioneered the use of deep-tank fermentation to manufacture penicillin at scale.[4]
- Today, penicillin and other antibiotics are still produced in water using industrial-scale bioengineering processes.[1]
- Advances in genetic cloning and vector/ plasmid insertion into microorganisms have increased yields and efficiencies of antibiotic production.[1]

In this closing example, molecular biologists, inspired by the chemistry of Nature, capitalized on a chance observation in ecological "warfare," ultimately hunting down the molecular culprit and uncovering new ways to make volumes of a breakthrough medicine. All of this seemed daunting at the time of Fleming's initial mold discovery.

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[1] Demain, Arnold L and Sanchez, Sergio, 2009, Microbial drug discovery: 80 years of progress, *The Journal of Antibiotics* https://www.nature.com/articles/ja200816

[2] Science History Institute Museum & Library, https://www.sciencehistory.org/education/scientific-biographies/alexander-fleming/

[3] Tan, Siang Yong MD, JD and Tatsumura, Yvonne MA, MD, 2015, Alexander Fleming (1881–1955): Discoverer of penicillin, Singapore Medical Journal, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4520913/

[4] Ginsberg, Josh, 2008, Development of Deep-tank Fermentation- Pfizer Inc., American Chemical Society Office of Communications, https://www.acs.org/education/whatischemistry/landmarks/penicillin.html

Chapter 3: The Ensemble Effect, Enhanced

Dr. Lester Grinspoon (1928 – 2020), a prominent Harvard psychiatrist and cannabis researcher, advocated for the concept of the "ensemble effect" rather than the more commonly used "entourage effect" when describing the synergistic interplay of cannabis compounds once they enter the human body.[1]

According to Dr. Grinspoon, the ensemble effect refers to the combined action of various components in cannabis, including:

- THC (delta-9 tetrahydrocannabinol)
- CBD (cannabidiol)
- Additional minor cannabinoids
- Terpenes, flavonoids, and other phytochemicals

He emphasized that the therapeutic benefits of cannabis are best achieved through the interaction of all these compounds working together, rather than isolated components.[1, 2]

Dr. Grinspoon argued that the ensemble effect is the reason whole-plant cannabis preparations are reported to be more effective than synthetic alternatives like Marinol (a THC-only pharmaceutical).[2] He believed that a full spectrum of plant metabolites creates the potential for more balanced and beneficial effects compared to individual phytocannabinoids.

Combining Natural and Synthesized Cannabinoids

Researchers are exploring the value of combining natural cannabis extracts with synthetic cannabinoids and other man-made compounds:

- Clinical studies have looked at combining CBD with synthetic CB2 receptor agonists to enhance anti-inflammatory effects.
- Additional research has explored adding synthetic terpenes to cannabis formulations to modulate their effects. Terpenoids are well-known to be bioactive on their own, but one issue that comes with the use of natural terpene distillates is that they exist as broader mixtures of alkene isomers.
- There is rapidly expanding interest in developing hybrid molecules that combine structural elements of phytocannabinoids with compounds designed to target protein receptors more selectively.

The rationale for uniting whole plant extracts with synthetic replicas and derivatives includes:

1. Enhancing or modulating the binding effects of naturally occurring cannabinoids
2. Improving the water solubility, bioavailability, and pharmacokinetic properties of these substances
3. Reducing unwanted side effects, such as psychoactivity, euphoria, drowsiness, etc.
4. Creating more selective or targeted therapeutic effects

Some key challenges encompassing this area of research include:

- Regulatory hurdles around the combination of natural and synthetic compounds
- Difficulty in standardizing whole plant extracts due to variabilities around growth or harvest conditions as well as processing operations
- Potential for unexpected interactions among multiple components
- Maintaining consistency in formulations derived from botanical sources and crops that are inherently never the same

Moving forward, more intensive research is needed to:

1. Systematically evaluate combinations of bioactive terpenes with synthetic cannabinoids
2. Assess the safety and efficacy of hybrid or blended natural-synthetic product formulations
3. Develop standardized protocols for combining products with consistency and control
4. Explore synergies between phytocannabinoids and designed CB receptor modulators

While promising, this remains an emergent field only in its infancy, requiring further scientific investigation to reach its full potential for therapeutic applications. There are growing expectations around research under the prospect of the US DEA's rescheduling of cannabis from Schedule I to Schedule III. Those interested in determining how various constituents of the plant, including trace components, impact bioavailability and efficacy – either positively or negatively – are surely going to look at enhancing formulations with lab produced materials just as we have seen throughout time in the realm of drug discovery.

A published article, "Cannabis and Cannabinoid Drug Development: Evaluating Botanical Versus Single Molecule Approaches," in *International Review of Psychiatry* [3] does a great job of comparing therapeutic development with botanical sources to those obtained synthetically, and it also reveals how combining such efforts is of special interest.

The following are some highlights from the article:

I. **Common misconception**: There are differences in the effects of a single molecule (*e.g.* CBD), depending on whether it is obtained by a laboratory synthesis or from an enzymatic synthesis occurring inside of the plant.
    a. A stereocontrolled chemical synthesis of (-)-CBD would make the same enantiomer (optical or chiral isomer) that the plant creates biochemically.
    b. Because the output molecules are identical in all respects, there can be no difference in how these ligands bind to CB1, CB2, or other protein receptors. As the authors point out, this must be true because "…chemistry is an exact science with respect to chemical composition and structure."
    c. The only circumstance by which meaningful differences in efficacy (between natural and synthetic materials) could manifest themselves would be from trace or minor components found in a botanical mixture or from "missteps in the synthesis of the cannabinoid," such as the presence of a minor stereoisomer.

II. A botanical drug, such as Epidiolex (CBD), requires clear and definitive characterization of its chemical makeup and the ratio of any ancillary components relative to one another. The chemist's ability to unambiguously define, demonstrate, and reproduce consistency in chemical composition is one of the significant roadblocks to botanical drug development, but at the same time it's one of the hallmarks of a well-optimized chemical synthesis.

III. Due to so-called "drug-drug interactions" a positive clinical outcome achieved "…for one defined botanical cannabis product cannot be generalized to other chemovars, or to cannabis more broadly. Similarly, lack of efficacy for one cannabis chemovar cannot be used to establish lack of efficacy" in general, "because the interactive effects of individual components of the botanical may negate effects that would otherwise be observed if cannabis with a different chemical profile was utilized."

IV. Overall, "synthetic drug development simply offers more choices"…and potential for greater precision than what is available with respect to naturally occurring phytocannabinoids. We wholeheartedly agree with this assertion, since synthesis and semi-synthesis can directly replicate any single molecule of known identity. Only when analytical chemists take on the painstaking task of purifying out discrete molecules from within a whole plant extract does the botanical approach align with synthesis, and this comes with additional issues around time, economy, and practicality.

V. In sum, while there appears to be tremendous therapeutic potential for cannabinoid medicines, there is a need for the development of defined, consistent, targeted and high-quality products. Independent of whether these are botanical or single molecule substances, these products must pass established standards for quality, safety, and efficacy before being approved for use.

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[1] Thompson, Rick, 2016, The Ensemble Effect, Not the Entourage Effect, Says Dr. Grinspoon, Komorn Law website (https://komornlaw.com/the-ensemble-effect-not-the-entourage-effect-says-dr-grinspoon/ , based on an interview on PGT Episode #290- Legend- Dr. Lester Grinspoon (https://www.blogtalkradio.com/planetgreentrees/2016/03/11/pgt-episode-290-legend-dr-lester-grinspoon)

[2] Grinspoon, Lester MD, 2000, Cannobinopathic Medicine, RxMarijuana.com, https://rxmarijuana.com/cannabinopathic_medicine.htm

[3] Bonn-Miller, M. O., ElSohly, M. A., Loflin, M. J. E., Chandra, S., & Vandrey, R., 2018, Cannabis and cannabinoid drug development: evaluating botanical versus single molecule approaches. *International Review of Psychiatry*, *30*(3), 277–284. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6242809/

Chapter 4: A Preparative Approach Aligned with Nature: Biomimetic Synthesis

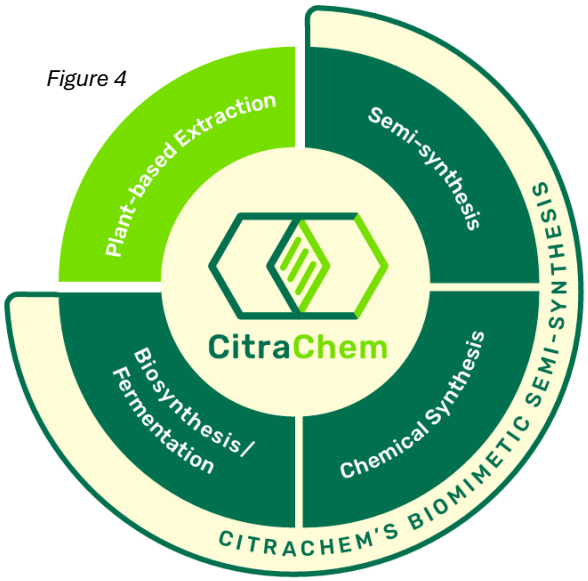
Biomimetic: the study of the formation, structure, or function of biologically produced substances and materials (such as enzymes or silk) and biological mechanisms and processes (such as protein synthesis or photosynthesis) especially for the purpose of synthesizing similar products by artificial mechanisms which mimic natural ones[3]

[3] *Merrian-Webster's Dictionary*

CitraChem was founded to find a cost-effective way to make ultra-pure single molecules that are *identical* to those synthesized within the plant or are derived from a further transformation, such as hydrolysis of a carboxylic ester to a cannabinoid acid. The acid or "A" form of well-known molecules such as CBDA and THCA are abundant in cannabis plants, especially at peak maturity when female plants are flowering. But their neutral counterparts are not dominant at this stage. This is because non-enzymatic decarboxylation takes place outside of the plant after harvesting. Due to instability in the presence of heat or sunlight, the acid forms of cannabinoids are more difficult to preserve than when produced and stored in a laboratory environment.

CitraChem's Co-founder, process Inventor and Chief Scientific Officer, Dr. Jason Kingsbury, has a passion for taking clues from natural systems. His years of training in the total synthesis of natural products led him to a deep appreciation for how higher plants, over millions of years, have evolved specific pathways for transforming metabolic precursors into the chemicals we know as cannabinoids. Dr. Kingsbury's fundamental discovery around processes that he could implement in a lab have resulted in patent filings that demonstrate a unique vision of applied chemistry that mimics the natural biosynthesis and results in molecules identical to the ones the plant produces.

Figure 4



In the previously shown Figure 3, a graphic depicts the four popular experimental processes used to access the full suite of *Cannabis* metabolites, including the genesis of products by organic synthesis and semi-synthesis. CitraChem's distinction is in borrowing aspects from three of the four possibilities and uniting them into a single strategy. Figure 4 depicts the melding of tactics that results in CitraChem's biomimetic semi-synthesis approach. The firm has found a way to take reactivity principles from plant biochemistry, select an appropriate alternative natural precursor, and then maintain a concise and direct approach to intended targets as is common in semi-synthesis.

The advantages of this biomimetic synthesis are clear:

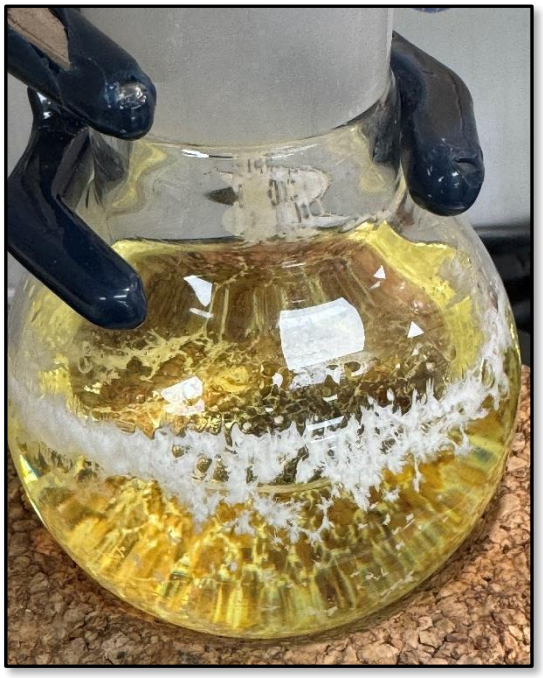
1. Without the need for botanically produced hemp or cannabis as a starting point, there is a significant reduction in the time and costs associated with growing cannabis crops, extracting harvested plant material to obtain appreciable quantities of cannabinoids, acquiring and maintaining specialized equipment, energy consumption, and water usage.

2. Even with a specific breed of plant and expert growing conditions, it is challenging to produce cannabinoids with identical quality and yield from different harvests.

3. Extraction processes require energy and chemical solvents. In addition, cannabinoids that are not plentiful in the plant (minors) make it too costly to extract in volume. Cultivators could breed rare strains in which those minors represent a higher percentage of the biomass of the plant. But growing specific strains based on chemical phenotype may or may not be efficient, given the trade-off of relinquishing grow space for potentially more valuable plants and finished goods.

4. After chemical extraction, the resulting cannabinoid oil mixture may still exist in a crude form that includes contaminants from the cultivation process. Any pesticides/insecticides that were applied, mold or mildew from humidity, and even heavy metals taken up by roots of the plants create additional purification expenses to achieve a high-quality outcome.

5. By using organic synthesis in a laboratory setting, target molecules can be produced on any desired scale completely free of the agricultural impurities listed above. Reagents used to modify starting materials and intermediates are much more easily removed in each operation because their chemical makeup and quantities (stoichiometries) are accurately known. Hemp and cannabis extraction solvents include supercritical CO_2, propane, butane, and hexane, as well as the common alcohols, ethanol and methanol.



6. Single molecules in any class – cannabinoids, terpenes, flavonoids, and more – produced in a controlled, laboratory setting by biomimesis, are as close to 100% pure as possible, free of other toxins or pathogens, and bear the exact same molecular structure as those made by the plant. And it goes without saying that access to unknown derivative molecules is simply impossible through cultivation but is very much in the realm of rapid possibility and reality with synthesis.

Conclusion

CitraChem's approach borrows from aspects of Semi-synthesis, Chemical Synthesis and Biosynthetic Fermentation techniques. The strategy employed is a unique blend of known processes that have historically been used to enhance natural ingredients for consumer products and for prescription drugs. CitraChem's novel biomimetic semi-synthesis approach to manufacturing respects the millions of years of botanical synthesis and celebrates how plants derive cannabinoid molecules naturally. By converting that knowledge to pathways that are controlled in a lab, starting with naturally derived base material and resulting in the exact same molecule as the plant produces, the biomimetic synthesized output is equivalently natural.

Botanical ingredients and medicines have been discovered, produced and leveraged for mankind's benefit over millennia. There is rarely a right or wrong answer about what to do with those discoveries. Should we leave them alone and use them as-is, or shall we find a way to streamline their mass production, render them even more bountiful while protecting our resources, and bring those benefits to the most people possible?

As cannabis entered the legal, regulated arena in the U.S. in the late 1990's, there was very good reason to expect that traditional cultivation, plant harvesting, processing of isolates or distillates, and administration of the active ingredients to users would be the best way to exploit the benefits of cannabis. After all, humans had been smoking and ingesting components of the plant for a very long time.

Given the potential of a controllable platform that yields the exact equivalent of a phytochemical, but in a manner free of any agricultural impurity or unknown adulterant that can taint the target compound, researchers, product formulators, and drug designers can continue to leverage the benefits of such a process towards a multitude of end products. They will be better able to create new remedies and therapeutic agents using precise combinations of inputs, raising the impact and role of a dominant molecule, yet still maintaining the ensemble effect where applicable.

As people strive to find alternative products and medicines to address an ailment or condition, we believe there is an underlying obligation to discover what exactly it is about cannabinoids, terpenes and flavonoids that positively impact the well-being of all humans. In the end, it shouldn't boil down to an "either or" choice. Just like prescription medications that are packaged in various ways to deliver the most efficient clinical outcomes, cannabinoids will be used in multiple forms as well. CitraChem's intent is to provide the highest quality compounds and therapeutic ingredients across the traditional medicine, consumer products, and pharmaceuticals landscape. Continued, relentless research is needed to determine which components do what and what combination of components yield the best results. Beginning with ultra-pure, single molecules is an important stage of the ongoing cannabinoid ingredient revolution.

About CitraChem

CitraChem Corp.™ has developed a biochemically inspired, organic semi-synthesis platform that produces phytocannabinoids and terpenes with high purity and stereoisomeric control. Our goal is to deliver cost-effective building block compounds, consumer product ingredients, and Active Pharmaceutical Ingredients (API) in order to accelerate medical research, facilitate drug development, and improve safety and quality across product types.

The company was founded to bring a process chemist's success in designing an efficient laboratory process for manufacturing high purity cannabinoids beginning with readily available plant-based terpenes. The starting point was to synthesize cannabidiol (CBD) following a pathway that mimics how phytochemicals are formed indigenously in all plants of the Cannabis genus. The route passes through cannabidiolic acid (CBDA) as an intermediate, which itself is difficult to procure in quantity and high purity as a botanical isolate due to its tendency to decarboxylate.

Subsequent work has shown the platform to be general, yielding other clinically relevant therapeutic agents in a fraction of the time and cost relative to fermentation-based and agricultural extraction approaches. CitraChem's long-term strategy is continuous innovation in developing processes to manufacture natural products, chemical building blocks, and research standards for designated target markets.

CitraChem's first commercially available ingredients will be offered under its PhytoCules™ brand which represents the output from the patent pending biomimetic semi-synthesis processes described in this white paper.