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Cannabis biosynthesis

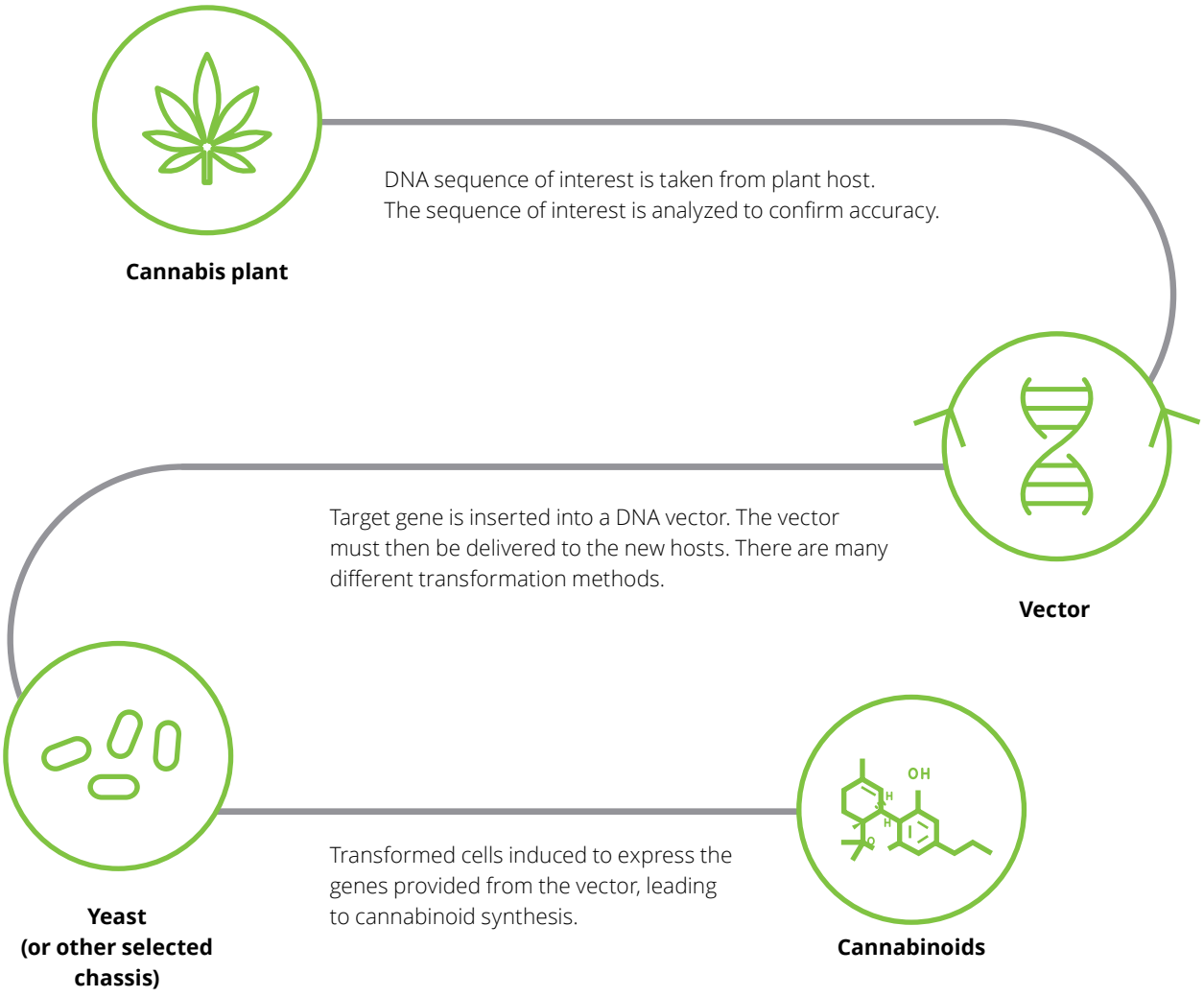
A promising new opportunity for life sciences companies

Contents

For decades, life sciences companies have used biosynthesis to produce a range of pharmaceutical therapies, including insulin, blood-clotting factors, and human growth hormone. More recently, researchers have also begun to explore how biosynthesis can be used to accelerate the production of cannabinoids such as tetrahydrocannabinol (THC) and cannabidiol (CBD). At first, this research might seem most useful to the cannabis sector, especially with regard to cannabis edibles and other alternative products. But cannabinoid biosynthesis offers an attractive opportunity for life sciences companies as well: it could result in effective—and profitable—new therapies.

Biosynthesis in brief

Figure 1: Simplified overview of the steps in creating a microbial host for cannabis biosynthesis



Biosynthesis is the process of genetically modifying an organism to produce biologically active compounds. There are a number of techniques and technologies used in biosynthesis, and new ones continue to emerge. While yeast, bacteria, and fungi are commonly used as host organisms in biosynthesis, others, such as microalgae and even animal tissue cultures, are being explored.[1]

A simplified example of one technique for biosynthesis is illustrated in Figure 1. In broad terms, scientists begin biosynthesis by identifying and extracting a gene of interest. They insert this gene into a DNA "vector," also known as a plasmid, which contains tools that enable it to transform a host organism (e.g., yeast). The vector/plasmid is then delivered to the host; the host is then allowed to grow in a media supplemented with compounds that help the host express the gene of interest.

Lab-based biosynthesis offers advantages over traditional production processes: it's more efficient and cost-effective, uses fewer resources, and provides more opportunity for quality. For example, when E. coli-derived insulin synthesis was commercialized, it replaced a traditional process that required thousands of pig and cattle pancreases to produce a fraction of the amount of insulin available today. The biosynthesis of insulin has saved millions of lives by delivering the quantity and quality of insulin the world needed while greatly reducing the cost of production and the resources required.

The cannabinoid biosynthesis frontier opens

In 2019, scientists at the University of California, Berkeley discovered how to genetically engineer ordinary brewer's yeast to produce both THC and CBD, the principal cannabinoids found in the cannabis plant, using a process similar to that described above. The researchers also produced novel cannabinoids not found in the plant.[2]

Why should this interest the life sciences sector? Because while there is anecdotal evidence that cannabis may have some benefit in treating a variety of conditions, from pain and inflammation to stress, sleep disorders, and more, a lack of clinical study has prevented stronger, science-based claims from being made.[3] Certainly, cannabinoids have been shown to function on the endocrine system and the brain. Epidiolex, a CBD-based prescription medicine, has been approved for use to treat two rare forms of epilepsy[4] and is being studied for use in treating other conditions.

Beyond that, however, there is much to be discovered, in no small part because scientists continue to learn more and more about the endocannabinoid system that THC and CBD affect. Endocannabinoids, molecules produced by the human body, were first discovered in 1992. The function of the endocannabinoid system is to maintain bodily homeostasis, or biological harmony in response to changes in the environment, and subsequent research has found that the endocannabinoid system is involved in a wide range of processes, from pain, memory, mood, and appetite to stress, sleep, metabolism, immune function, and reproduction.[5] For life sciences companies, the endocannabinoid system is both a rich research field and a potential path to countless new therapies.

Biosynthesis provides life sciences companies with the means to explore cannabis' health and wellness potential— not only of THC and CBD, but of the dozens of minor or trace cannabinoids that can only be extracted in extremely low concentrations naturally. These rarer cannabinoids would be virtually impossible to produce at scale using traditional methods, owing to the sheer quantity of cannabis that would need to be cultivated. Moreover, the biosynthesis process itself can result in novel molecules that, while they may appear similar to cannabinoids, will have unique chemical and potential biological properties. Whether natural or lab-created, these compounds have the potential to become the basis for new therapeutic agents.

Could cannabinoid-based therapies replace traditional pharmaceuticals?

Researchers at the University of Victoria have found that nearly 70 percent of medical cannabis patients consumed cannabis as a substitute for prescription drugs, particularly opiates/opioids, antidepressants and anti-anxiety medications, and non-opioid pain medication.[7]

The biosynthesis advantage

Current methods of manufacturing cannabinoids are highly traditional and resource-intensive. Massive quantities of cannabis plants must be planted, grown, and harvested, with cannabis cultivated indoors requiring large capital investments and energy costs. THC, CBD, and other cannabinoids must then be extracted and purified. The entire process is costly and inefficient, and because the process often produces compounds with highly variable chemical composition, it also delivers inconsistent product quality. Biosynthesis, on the other hand, allows cannabinoids to be developed in batch runs under highly controlled conditions, greatly improving quality consistency—at lower cost.

What's more, the sheer number of active cannabinoids in the cannabis plant have made it difficult for researchers to determine whether a particular effect is produced by a single component within cannabis or is the result of synergies between many. Isolating single cannabinoids through biosynthesis, on the other hand, enables researchers to directly correlate cause and effect; this offers life sciences companies an advantage in terms of drug discovery.

Comparing cannabinoid production methods

Traditional production	Biosynthesis[6]
Three-month growing season grown outdoors during three-month growing season or indoors using heat lamps, ventilation fans, etc.	**Year-round growing season** grown year-round in lab using genetically engineered bacteria or another host organism
4 to 6 harvests/year using indoor cultivation	**23+ harvests/per year** per bioreactor
Variable quality due to environmental factors, pests, genetic drift	**Consistent quality** due to controlled lab environment
95% of plant biomass wasted	**0%** plant waste
16-tonne yield from 1-million square foot greenhouse	**1,000-tonne yield** from a similar-sized production facility
Variable purity	**99% purity**
$5,000/kg CBD cost	**<$1,000/kg** CBD cost

The challenges can't be overlooked

While cannabinoid biosynthesis holds a great deal of promise for both cannabis and life sciences companies, there are still challenges to overcome. Many organizations and institutions have invested in cannabinoid biosynthesis research, tools, and processes. Much of the work to date is purely academic research—experimental, proof-of-concept efforts conducted at small scale and producing minute amounts of cannabinoid compounds.

Part of the challenge is host related. Researchers may spend a great deal of time—months—working with a particular host organism, only to discover that the host doesn't produce the expected or desired results. Different hosts provide different environments, and these environments shape the behaviour of the enzymes involved in creating cannabinoids and add something of an "individual flair." As well, cannabinoids have been found to be rather toxic to their host organisms, sending researchers hunting for microorganisms that are able to withstand higher toxicity levels, such as algae and the microorganism involved in producing tequila. Developing hosts capable of large-scale cannabinoid production can be an incredibly slow process. Each gene added to the target host must be evaluated through multiple stages, which takes time to complete, and the output must be screened for target molecules.

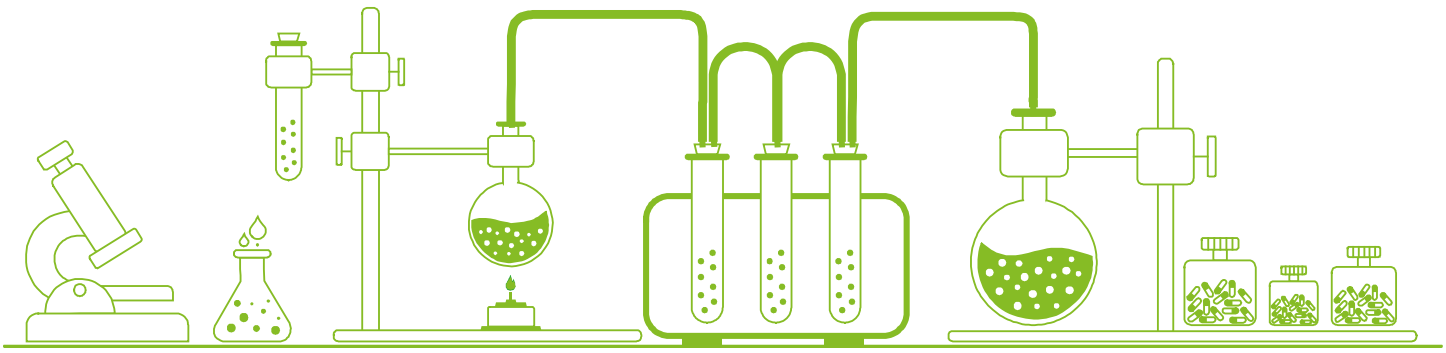
Even when a promising host is found, scaling up can be very difficult. A bioreactor that can reliably produce a small amount of compound may be unable to reach the larger yield necessary to make the effort worth it. Moving to a larger production environment can also introduce unexpected quirks and problems: temperature micro-fluctuations in a 25-litre continuous culture system, for example, may cause host organisms to exhibit different behaviours and express different compounds.

Life sciences firms can capitalize on the lessons learned in Canada

Since legalizing recreational cannabis in limited forms in 2018, and with the subsequent expansion of cannabis edibles and other alternative products in 2019, Canada's cannabis sector has learned many lessons. It also remains at the forefront of the global cannabis industry, having the expertise, the experience, the access to capital, the academic research partnerships, and the regulatory framework necessary to enable life sciences companies to capitalize on the opportunity and invest in cannabinoid biosynthesis research.

Companies around the world can look to Canada's experience to accelerate their own cannabis infrastructure and biosynthesis.

Other countries have followed in Canada's footsteps, legalizing cannabis for medical and recreational purposes, and there will be more to come. Research into cannabinoid biosynthesis will pick up pace, and clinical trials will inevitably follow. As research accelerates, discoveries of cannabinoid-based therapies will most surely follow.



Key considerations for launching a cannabinoid biosynthesis program

Cannabinoid biosynthesis holds tremendous potential for life sciences companies in their quest to discover new compounds that could hold the key to effective, profitable pharmaceutical therapies and other products. With research still in its infancy, now is an ideal time for life sciences companies to invest in the field and put more ground between themselves and their competitors.

However, there are key considerations to contend with in launching a cannabinoid biosynthesis program, including:

Obtaining the correct licensing

Before research begins, companies will need to obtain the required licensing from the appropriate regulatory authorities. They may find that biosynthesis falls into something of a licensing grey area. In Canada, for example, companies theoretically require a standard or micro-processing licence, or a research licence to extract cannabinoids from the cannabis plant, although at the time of writing, we're unaware of any company receiving a micro-processing license for the purposes of biosynthesis. Cannabinoid biosynthesis generally takes place under the umbrella of research and development activity, which is subject to protocols submitted to regulatory authorities. A life sciences company could submit a broad protocol, for example, but be licensed to only perform those activities it has stated in its protocol.

Choosing the correct host

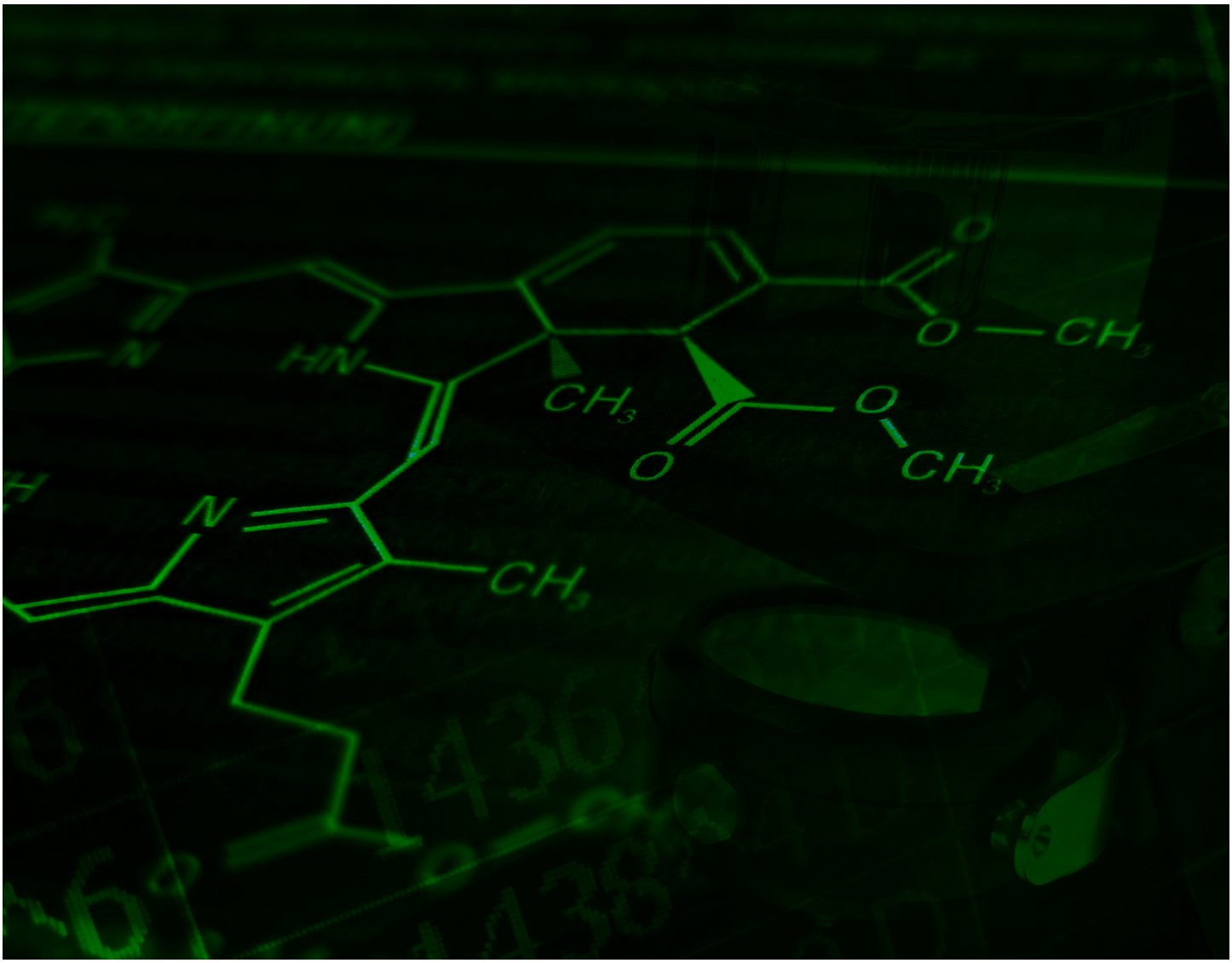
Life sciences companies have a wealth of options when it comes to choosing a host organism for biosynthesis research, from bacteria to algae and beyond. Of course, the nature of scientific research means that the host selected may not work in the end, due to issues related to yield, toxicity, scalability, or other matters. Company leaders should therefore work with their scientists to establish a clear rationale for choosing a given host. They should review the relevant literature, speak with subject matter experts, and learn from and avoid others' missteps and errors before committing to a course of action and inquiry.

Conducting clinical trials

Consumers may claim that cannabis provides many health and wellness benefits, but regulators are much more skeptical. As a result, life sciences companies whose biosynthesis research successfully produces a cannabinoid will still need to conduct clinical trials in order to clearly establish that the cannabinoid does in fact treat a given condition or deliver a particular health benefit. Before they can launch clinical trials, however, they must receive authorization from the relevant governing health authority. Additionally, material used in clinical trials beyond phase one studies may need to be produced at a level adhering to the good manufacturing practices used in pharmaceutical facilities.

Explore the opportunities of biosynthesis

Recent advances in cannabinoid biosynthesis are opening new pathways to discover new compounds with the potential for use in health and wellness applications and, most importantly, new pharmaceutical therapies. Moreover, biosynthesis can enable companies to produce these cannabinoids at a cost, consistency, and quality traditional cultivation methods can't match. Now is the time for life sciences companies to invest in cannabinoid biosynthesis and begin their own journey of discovery.



Endnotes

1. *Vavitsas, K., Costa, K., Limas, M., Joseph-Nelson, B., and Cumbers, J. "Cannabinoid Fermentation: Scalability, Purity, and Sustainability for an Emerging Market."* https://geneticliteracyproject.org/wp-content/uploads/2019/06/Cannabinoid-Fermentation-SynBioBeta-Industry-Report-June-2019.pdf. Retrieved May 24, 2020.

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