Cannabinoid Fermentation:
Scalability, Purity, and Sustainability for an Emerging Market

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1. Executive summary

Investors poured $10 billion into North American cannabis companies in 2018, in anticipation of a $16 billion market in 2019[1]. Why?

The recent legalization of cannabis in certain parts of the United States and in Canada, combined with new research findings about the health benefits of cannabinoids, has generated huge commercial interest. The interest is growing not only in the cannabis industry, but also on the periphery where other "social lubricants" such as alcohol face the threat of reduced demand as consumers now have other choices with sometimes more desirable attributes. **In addition to recreational markets, cannabinoids are increasingly recognized for their therapeutic uses**, which are only becoming apparent now that it is becoming destigmatized and legalized for scientific research

With the growth in the market comes a need for, well, growth - of the volumes and methods for producing cannabinoids. Conventional cannabinoid production involves growing cannabis outdoors, in greenhouses, or in dedicated indoor grow facilities. The flowers (leaves) are then harvested and the active ingredients are isolated using chemical solvent extraction processes. This agriculture-based process requires significant light energy, chemical fertilizers, and chemical purification of cannabinoids. It is also limited by the slow growth cycles of the plants themselves, where the cannabinoid content may vary by as much as 300% from cycle to cycle, even in a "controlled" indoor environment.

A new and better means of growing cannabinoids is brewing - microbial fermentation. Also known as biosynthesis in the production of consumer goods, it's a faster, more efficient, and more sustainable solution to cannabinoid production and many other products where high precision, purity, and sustainability are desired.

This report examines how microbes can be used for the fermentation of cannabinoids, the advantages of biosynthesis over traditional plant extraction, and how biotechnology promises to provide industrial-scale solutions to this fast-growing market.

[1] https://www.cnbc.com/2018/12/27/legal-marijuana-industry-had-banner-year-in-2018.html

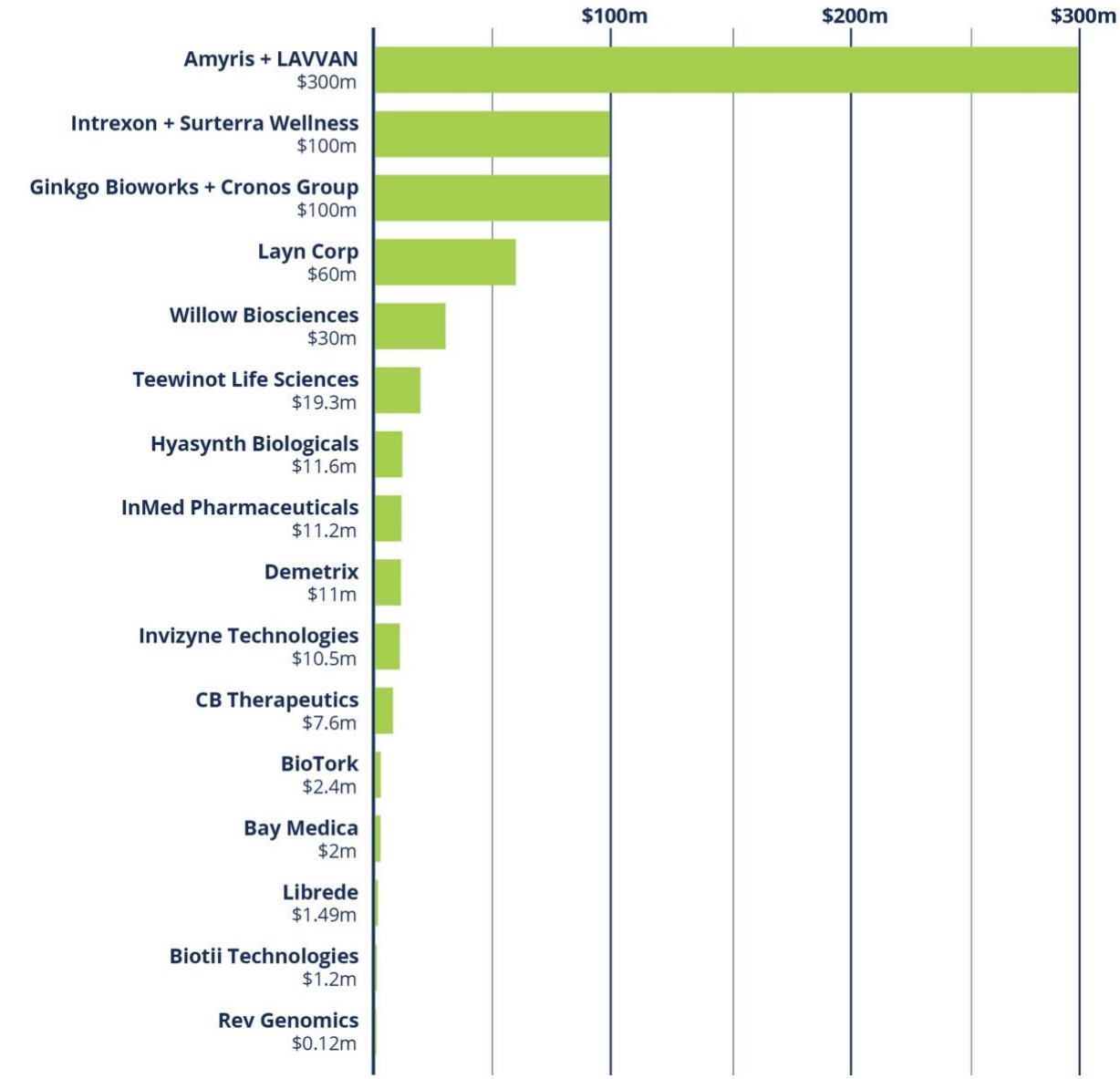


Figure 1: Investments in biotechnology cannabinoid-producing companies. In cases where company investments in cannabinoid production have not been made public, no data is shown. Source: SynBioBeta.

2. What are cannabinoids, and what are their uses?

Before we explore how cannabinoids are produced, it can be helpful to understand how they are used, and why that usage is set to grow for not just recreational, but also health and medical uses.

THC and CBD are the two key cannabinoids. Cannabinoids are a diverse family of more than 110 known compounds produced naturally in many organisms, (including humans).[2] The better-known and best-studied cannabinoids are Tetrahydrocannabinol (THC), which has the psychotropic (euphoric) effects associated with "pot", and the non-psychotropic Cannabidiol (CBD), which is used associated with many new consumer goods, claiming a variety of benefits from mood enhancement to sleep. In addition to CBD and THC, many others are found (but in very low quantities) in cannabis plants[3], and each plant produces a combination of cannabinoids which varies depending on their growth environment and plant variety.

Each cannabinoid has different effects and interactions that scientists are just starting to understand. They can be broadly divided into two classes: psychoactive and non-psychoactive. These chemical compounds act on the cannabinoid receptors found in the brain (CB_1) and in immune system cells (CB_2)[4] of humans and animals. But little is known about their benefits, since for many years, marijuana use has been socially stigmatized and marked as a non-conforming behavior. Scheduling of the compounds by the US Drug Enforcement Agency -- and the resulting public interpretation of regulations around cannabis -- has discouraged scientists and investors from pursuing research and commercialization around the positive therapeutic benefits of cannabinoids. Furthermore, the proliferation of cannabinoid-containing consumer products in a generally unregulated marketing environment has increased confusion among potential and current consumers.

[2] Humans produce their own endogenous cannabinoids, such as Anandamide and 2-Arachidonoylglycerol.
[3] https://pubs.acs.org/doi/10.1021/acs.jnatprod.5b00949
[4] https://en.wikipedia.org/wiki/Cannabinoid

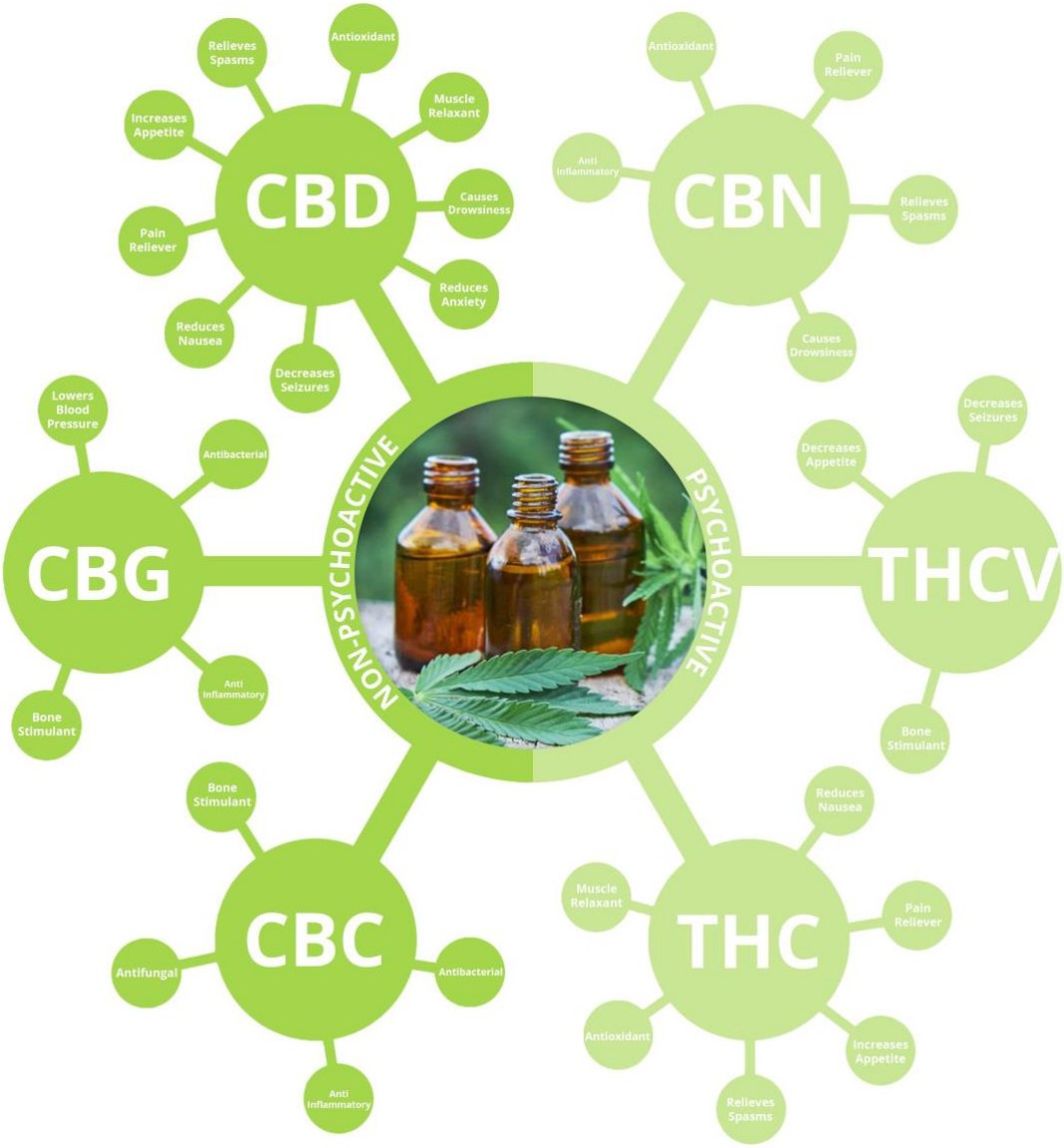


Figure 2: The best understood cannabinoids and their uses. Adapted from CBDNerds.org.

3. Health effects of cannabinoids

The cannabinoid with the best understood pharmaceutical properties is CBD. According to the US National Institutes of Health, CBD is used in preliminary studies of anxiety, cognition, movement disorders, and pain[5]. It has a proven therapeutic value in psychiatric disorders[6] and is FDA approved as the drug Epidolex for the treatment of epileptic disorders Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS).[7] The other well-known cannabinoid, THC, has been found to have health benefits such as multiple sclerosis symptoms relief[8], as well as appetite stimulation and cachexia[9]. THC has shown low potential as a drug for neurodegenerative and other neurological disorders[10]. Synthetic forms (marketed under the brand names Dronabinol and Marinol) have been approved by the US FDA to treat CINS (cancer-induced nausea and vomiting).

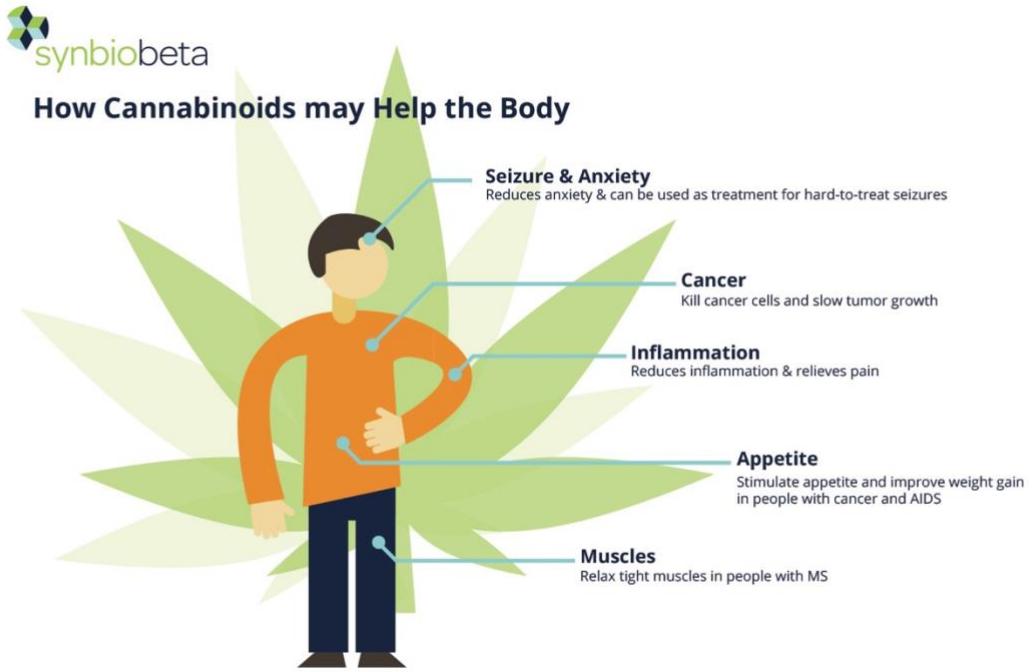


Figure 3: Potential health benefits of cannabinoids. Adapted from webmd.com.

[5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5719112/
[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4707667/
[7] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[8] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4011465/
[9] http://www.jcancer.org/v10p0716.htm
[10] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4011465/

The National Academy of Sciences summarize several areas where cannabinoids may have a medical benefit, such as chronic pain, opioid addiction (see also NIDA), respiratory disease, immune system diseases, and mental health. For these conditions, the effects of cannabinoids are modest; for all other conditions evaluated, there is inadequate information to assess their effects[11]. There is some caution suggested as cannabis use is linked with substance abuse. However, as the societal attitude on cannabis and the legal framework change, there is more and better research on potential health benefits of cannabinoids[12].

4. Cannabinoid fermentation

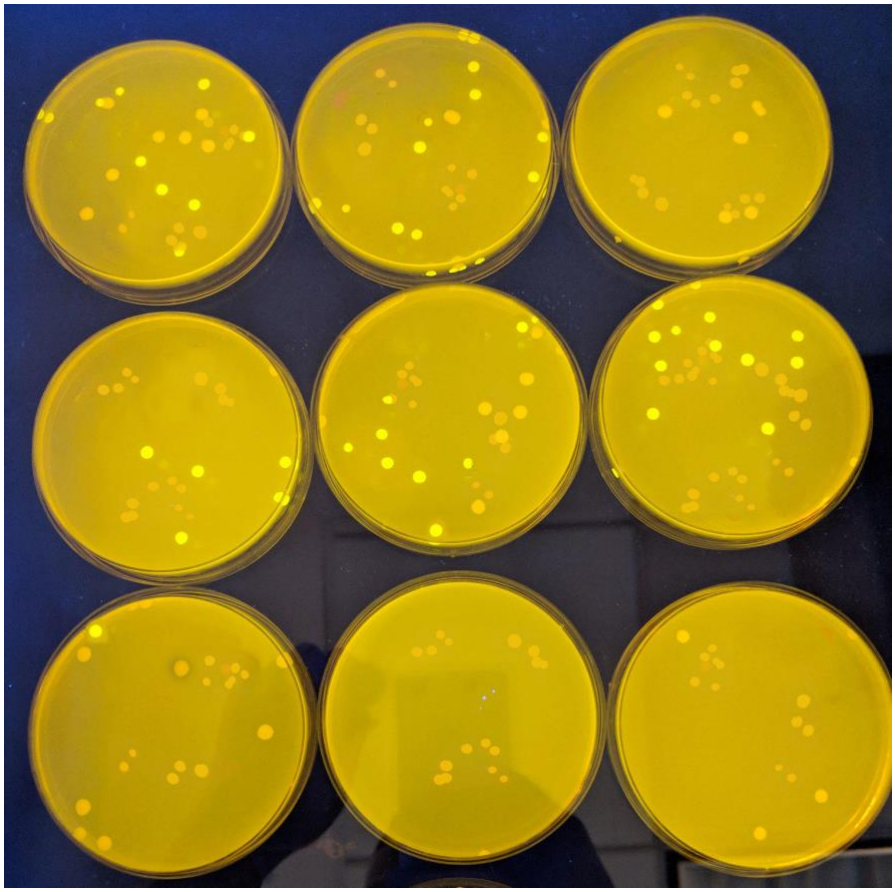
As medical research expands, the need for medical-grade cannabinoids does as well. The complex regulatory framework and restrictions on plant-derived cannabinoids may discourage researchers from pursuing preclinical studies. In addition, there are major differences in the clinical effects when using unrefined plant extracts compared to purified cannabinoids.

Cannabinoids are traditionally produced via a chemical solvent extraction of cannabis plant flowers (more on this below). However, in early 2019, UC Berkeley researchers produced THC and CBD in brewer's yeast[13]. This is the most recent published work showing that it is possible to move cannabinoid metabolic pathways from a plant into a microbe.

Microbial fermentation of cannabinoids has the following advantages:

- Cheap fermentation of the active ingredients
- Continuous production (versus slow plant growth and harvest cycles)
- Controlled production of specific cannabinoids
- Precise determination of the compound mix
- Production of "rare" or new cannabinoids found in little or no amounts in the plant
- Higher consistency and reproducibility
- Less complex post-processing requirements
- More environmentally sustainable production process (i.e., reduced land, water, and energy use)
- No need for pesticides
- No toxic heavy metals used in fermentation

[11] https://www.nap.edu/resource/24625/Cannabis_chapter_highlights.pdf
[12] https://www.nature.com/articles/d41586-018-07037-1
[13] https://www.sciencedaily.com/releases/2019/02/190227131838.htm



UC Berkeley researchers have reconstructed within yeast the metabolic pathway that produces the active ingredients of marijuana -- CBD and THC. It also allows for the production of any of the more than 100 other cannabinoids produced by plants in tiny amounts, as well as new cannabinoids with improved pharmacological properties. Jay Keasling, a UC Berkeley professor, co-founded a spinout, Demetrix Inc., that licensed the technology from Berkeley. Source: Demetrix.

5. Why fermentation? Why now?

Fermentation is clearly advantageous for producing cannabinoids in health and medicine, and it can fill the need for a large and growing market for low-cost, high-quality cannabinoids beyond medicine as well. The legalization of cannabis for both medical and

recreational use has resulted in the explosion of the cannabis and related industries, which is predicted to reach a market size of $57 billion by 2027 in the US[14]. The global market, as estimated by New Frontier Data, is today valued in excess of $340 billion USD[15]. As the market increases, so does the need for low-cost, high-quality cannabinoids. There are several reasons fermentation can help.

The economics of plant-based production are unfavorable. Labor and land costs may make it economically unfeasible to build out even large-scale cannabis facilities in the U.S. Analysts such as Kris Krane from 4Front believe that, in the long term, "it will be simply untenable for large-scale indoor cannabis producers in the United States and Canada to survive. Even greenhouse producers in most regions of the country will struggle to compete with low-cost production on the west coast and Latin America."[16]

Fermentation technology is proven and cost effective. It is common practice for synthetic biology researchers and their companies to recreate a plant's natural product metabolic pathway in microorganisms for high quantity, low cost, scalable production. Large scale fermentation techniques are established and have a long track record of economic viability. The metabolic pathways leading to the synthesis of THC, CBD, and some additional cannabinoids such as cannabigerol (CBG) and cannabichromene (CBC) are well characterized. In addition, biosynthesis allows enzymatic engineering and modifications which could produce new-to-nature cannabinoids with improved pharmacological characteristics. Cannabinoid variants have different medicinal properties (e.g. the two stereoisomers of CBD, (+)-CBD and (-)-CBD, have different pharmacological effects[17]). These technological advantages make microbes an ideal candidate

> *"Few cannabis companies have the ability to target and produce rare cannabinoids and explore their benefit at meaningful scale… our proprietary platform is poised to cost-effectively produce specific cannabinoids at commercially relevant quantities and open doors for their researchers to fully explore the potential of cannabinoids."*
>
> Randal J. Kirk,
> CEO of Intrexon Corporation

[14] https://www.forbes.com/sites/thomaspellechia/2018/03/01/double-digit-billions-puts-north-america-in-the-worldwide-cannabis-market-lead/#43823a706510
[15] https://newfrontierdata.com/marijuana-insights/global-cannabis-market/
[16] https://www.forbes.com/sites/kriskrane/2018/04/25/cannabis-cultivation-will-be-a-race-to-the-bottom/#76a59bd04184
[17] https://www.fundacion-canna.es/en/cannabis-vs-thc-are-they-really-so-different

for controlled and precise fermentation, as the compounds produced using fermentation are identical to those produced by plants.

Price factors: Compounds such as CBD are marketed to consumers at retail prices sometimes in excess of $150/gram. To put this in perspective, an epileptic patient may require in excess of 1 gram/day of CBD, effectively pricing these products beyond the reach of most consumers. It should also be noted that a therapeutic dose of CBD can be 10 times greater than THC, creating even more pressure on retail prices. Further exacerbating the consumer dilemma is the marketing of products with very low concentrations of a cannabinoid, such as water that contains less than 3-5mg of CBD. Some experts argue that these concentrations will provide little to no therapeutic value, perhaps resulting in consumers concluding erroneously that CBD is ineffective for them.

6. Plant extraction versus fermentation

As industrial cannabis production ramps up, the cannabinoid industry faces the same question as biopharma, chemicals, materials, and others: Can biology do this better?

Plant-based cannabinoid production takes tons of material, energy, and time. The most common cannabinoid production method nowadays is solvent chemical extraction from cannabis plants, combined with additional post-extraction processing and distillation. This is a costly process that is time and resource intensive. Except for some strains that produce high levels of CBD or THC, cannabinoids comprise a small part of a plant's biomass, with the rare or "minor" cannabinoids produced at <1% levels. Furthermore, the process wastes a lot of plant material (biomass) and consumes a large amount of resources. Additionally, as suggested earlier, cannabis cultivation is energy consuming and environmentally unfriendly[18]. About 1% of US energy (and 3% of the state of California's) is used for the cultivation of indoor cannabis[19]. The production of the exact same compounds in microbes has a dramatically lower carbon footprint[20].

Plant yields vary widely, causing higher costs and risks. What's more, the cannabinoid content may vary by as much as 300% between different harvests, both in quantity and in

[18] https://www.theguardian.com/society/2017/jun/20/cannabis-climate-change-fossil-fuels
[19] https://merryjane.com/news/1-of-all-us-energy-used-to-grow-cannabis
[20] https://www.newcannabisventures.com/how-biosynthesis-of-cannabinoids-could-impact-the-cannabis-industry/

composition of the individual compounds. This means that health regulators may have trouble determining and more importantly guaranteeing the quality and effectiveness of plant extracts – a problem that could be solved by microbial production[21].

Outdoor farms need pesticides to keep plants pest-free. Outdoor growers are likely to confront pests. Indoor and outdoor growers both must use caution when using chemical pesticides, which could have toxic effects on the environment, the plants themselves, and cannabis consumers. As a general rule, experts mandate the deployment of pesticides clearly marked as "safe to use on food crops." The EPA has not registered any pesticides specifically for use on cannabis.[22] Furthermore, because of cannabis' illegal status until recently, industrial cannabis horticultural practice may be lagging behind that in established agribusiness. Microbial production also has the advantage of precision. Microbes can be engineered to produce an exact composition of cannabinoids which will be the same in each batch. Cannabis (in indoor cultivation conditions) can give six harvests per year, while a single bioreactor can give 23 batches in the same amount of time[23].

A 1 million square foot greenhouse growing cannabis plants might yield only 16 metric tons of cannabinoids per year. A fermentation facility of the same footprint and investment could generate in the neighborhood of 1,000 metric tons annually[24]. And according to Jay Keasling, fermentation uses "less land, smaller facilities and more limited manpower. Its waste product is mostly water, which can be safely treated with existing technologies that large-scale fermenters already use"[25].

[21] https://www.fool.com/investing/2019/03/01/will-cannabis-producers-ditch-greenhouses-for-bior.aspx
[22] https://www.epa.gov/sites/production/files/2017-10/documents/session-5-cannabis-status-update.pdf
[23] https://www.fool.com/investing/2019/03/01/will-cannabis-producers-ditch-greenhouses-for-bior.aspx
[24] https://finance.yahoo.com/news/cannabis-producers-ditch-greenhouses-bioreactors-200024309.html
[25] https://www.theatlantic.com/health/archive/2019/02/weed-active-ingredients-yeast/583765/

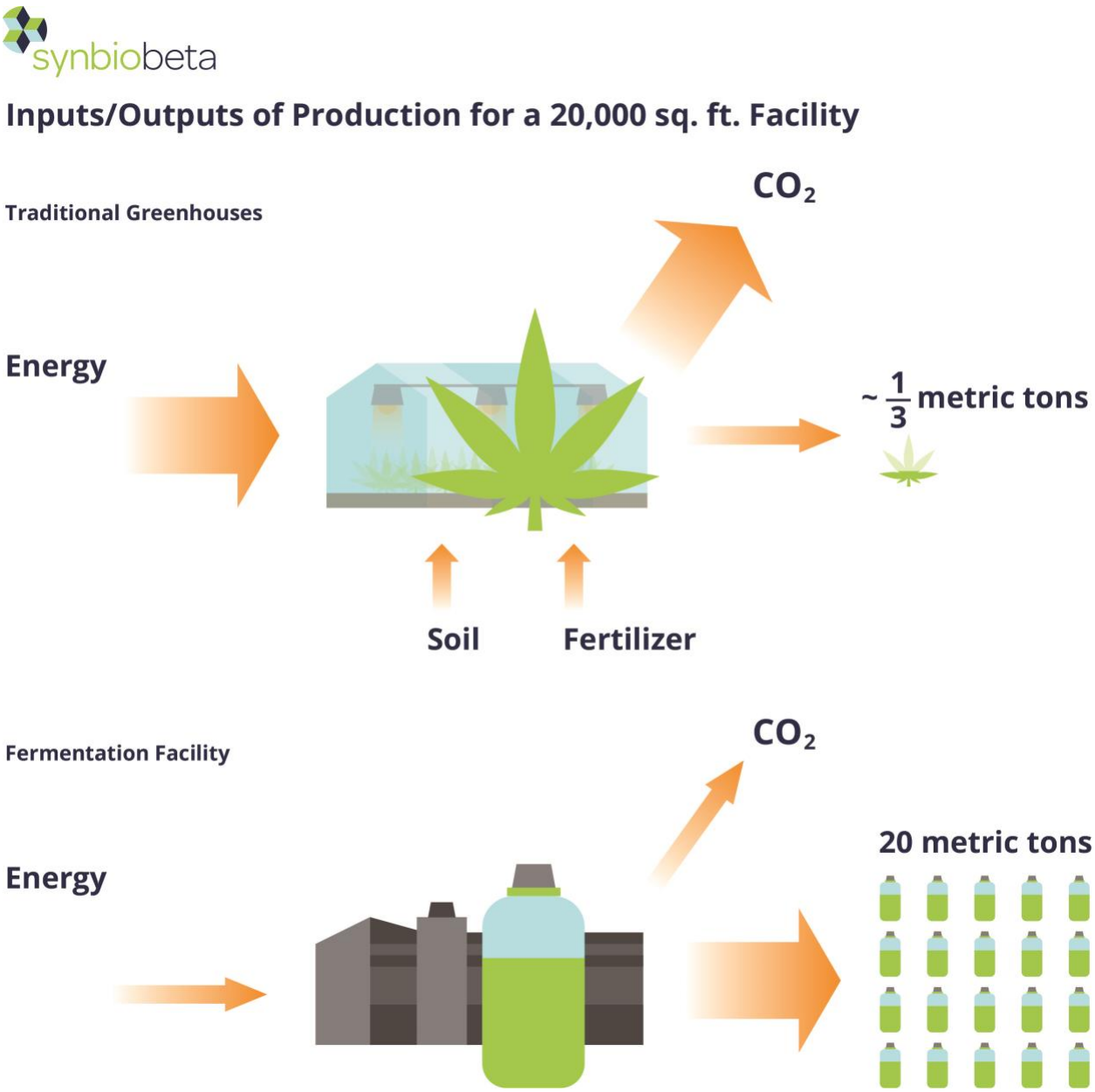


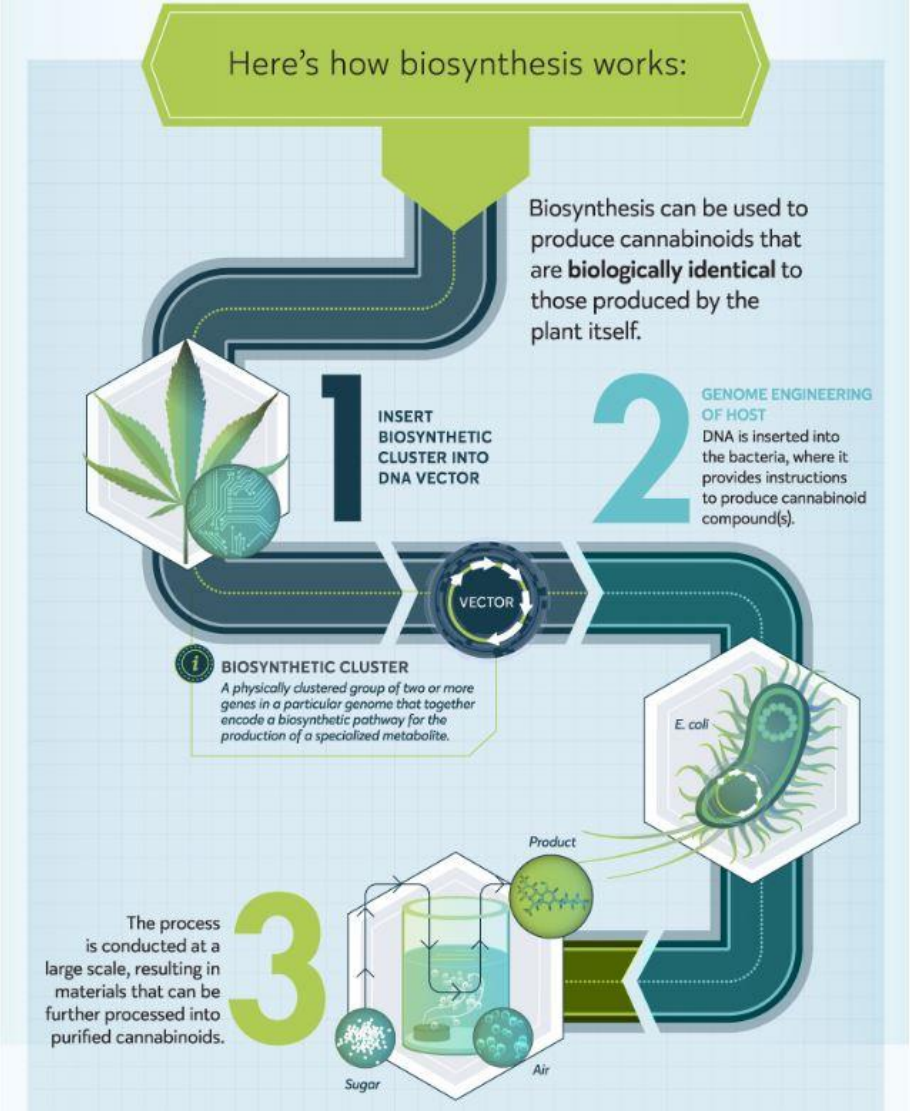
Figure 4: Cannabinoid production shows promise of a 60-fold increase in production using fewer resources. Source: finance.yahoo.com.

Fermentation is not projected to replace cannabis extraction completely, at least not in the short run. Producing CBD and THC in the lab is currently estimated to be **five to eight times more expensive** than extracting them from cannabis[26]. Most likely, microbial cannabinoids will supplement the plant-derived market with non-standard, rarer compounds of higher purity and bioactivity[27].

> *"We believe the industry is making significant progress over what has been publicly announced... Demetrix has accelerated production capabilities by several orders of magnitude from [our published results in Nature]."*
>
> *Jeff Ubersax, CEO of Demetrix*

[26] https://business.financialpost.com/cannabis/scientists-racing-to-create-lab-grown-synthetic-cannabinoids-but-cannabis-plant-not-obsolete-just-yet

[27] https://www.newcannabisventures.com/why-cannabinoid-biosynthesis-will-have-a-significant-role-in-fueling-the-growth-of-global-cannabis-brands/



How the genes that produce cannabinoids in plants can be inserted into microbes to biosynthesize specific molecules in bacteria. Source: InMed Therapeutics.

7. Technical challenges

Microbial production yields are so far small. The reported yields in yeast are in the low mg/L scale[28], and these yields should "***increase by at least 100-fold*** *for the cost to be competitive with plant-extracted cannabinoids*", according to Jason Poulos, chief executive of Librede[29]. Working with plant enzymes is not straightforward, as they are evolved to work in their natural hosts. Moreover, enzyme modifications are needed to increase their specificity and yields[30].

It could be that we are some time away from viable microbial production of cannabinoids, maybe another 18–24 months according to David Kideckel, a cannabis analyst with AltaCorp Capital in Toronto[31]. Nevertheless, many startups and big players of the synthetic biology industry are aggressively moving into the field, investing in and exploring cannabinoid fermentation.

> *"[When we started five years ago,] the biggest activity was towards research and legalizing access to Cannabis. Now, problems are coming with scaling the supply of cannabinoids, and researchers are really keen to find out how to make even better medicines based on cannabinoids."*
>
> Kevin Chen, CEO of Hyasynth

[28] https://www.nature.com/articles/s41586-019-0978-9
[29] https://www.nature.com/articles/d41586-019-00714-9
[30] https://www.chemistryworld.com/news/genetically-engineered-yeast-brews-up-heady-mix-of-natural-and-unnatural-cannabinoids/3010174.article
[31] https://www.nature.com/articles/d41586-019-00714-9

8. Legal and regulatory outlook

The legal and regulatory path is less clear than the technical challenges. Cannabis has been decriminalized in Canada and several US States, and the use of cannabinoids for medical purposes is legal in Germany and several other European countries. However, there are discrepancies in the American legal system regarding the regulation of cannabis extracts and cannabinoids[32]. For example, recreational use of marijuana is legal in the state of California for those 21 years and older, and it can be ordered online and delivered to your residence, even as it remains a Schedule I drug and is federally illegal.

Permits are required to begin researching cannabinoids, even in countries and states that have legalized access to cannabis. Companies like Ginkgo Bioworks appear to be working closely with regulatory agencies in order to receive clearance to start work.[33]

GW Pharmaceuticals conducted extensive clinical trials on the CBD drug Epidiolex® and received FDA approval for its use in the treatment of a number of epileptic-type disorders. FDA regulations stipulate that once a compound is scheduled as a drug, it cannot legally be considered a supplement or food product, which further complicates the landscape for producers of CBD products for consumer use.

On May 31, 2019, the US FDA held a public hearing to explore questions around topics ranging from safety to marketing claims, quality standards, concentrations, drug interactions, and dosing (see "Consumers, labeling, and bioengineered products" below). The FDA has an interest in protecting the efforts and investments made by companies researching and developing products. Presenters included representatives from the scientific community, the agriculture industry, manufacturers, retailers, health-care professionals, lawyers, and consumer and patient advocates. While many had hoped the meeting would clarify the regulatory environment, based on the exchanges between the FDA and stakeholders, it appears that for CBD in particular a solution is some time off. The FDA plans to accept more public comments this month through July 2.[34] Then it will begin to develop draft regulations and seek further input on those before any regulations are put in place.

[32] https://www.leafly.com/news/politics/cbd-oil-legal-depends-ask
[33] https://ir.thecronosgroup.com/news-releases/news-release-details/cronos-group-and-ginkgo-bioworks-announce-landmark-partnership
[34] https://www.regulations.gov/docket?D=FDA-2019-N-1482

At the hearing, New Frontier Data's Hemp Business Journal reported that CBD-related sales more than tripled between 2014 and 2017, to $367 million. It estimates that the market will grow to be worth $2.1 billion by 2020. It also reported that big players like Canadian cannabis producer Canopy Growth is building a hemp production facility in New York, and big pharmacy retailers like Walmart and CVS Health are stocking topical items (but not foods) on their shelves. In April 2019, Walmart announced a distribution deal with New Age Beverage Corporation, whose Marley Mellow Mood + CBD beverage will launch globally in 2019.[35] Well-known brands like Ben & Jerry's are also expected to make product announcements when the national regulatory landscape is deemed ready.

Market projections, deals, and product launches like those above may prove false unless regulation is put in place to remove uncertainties in making and selling cannabinoid products.

Medicinal grade cannabinoids are likely to be regulated in the same way as other pharmaceuticals. As such, there will be a need for clinical trials and a significant investment in establishing specific medical benefits for certain conditions. It may be expected that products containing one or a mix of cannabinoids that do not claim any therapeutic qualities could be regulated as food additives or nutritional/dietary supplements if they are proven to be safe at the use levels suggested on the product labels.

[35] https://www.marketwatch.com/press-release/new-age-beverages-corporation-expands-with-walmart-2019-04-08

9. Industrial players

Cannabinoid microbial production has attracted some major industrial players, and the biotech investments build up a significant momentum.

Amyris and **LAVVAN**, a newly-formed company, announced a $300 million deal to bring fermentation-derived cannabinoids to the market[36]. **Ginkgo Bioworks** signed a partnership with Cronos Group, in which the company will receive up to $122 million for targeting bioactive compounds of marijuana[37]. Both companies have a long history in using the yeast *Saccharomyces cerevisiae* as a platform for plant metabolic products. **Intrexon** announced that it has engineered yeast to produce cannabinoid compounds as well as a $100M partnership with **Surterra** to advance commercial scale cannabinoid fermentation[38,39].

The longest-established player in the cannabinoid biosynthesis field is the Canadian startup **Hyasynth Bio**. Also working in yeast, the company is a licensed dealer of cannabinoids, and aims to produce the compounds in large scale and in an eco-friendly manner. The San Diego-based biotech **Cellibre** has announced the yeast production of cannabinoids, in an efficient manner[40]. The UC Berkeley spinout **Demetrix,** founded by Jay Keasling, plans to commercialize their reported research, and have attracted $11 million of seed funding.

Purissima, a JLABS company, based in South San Francisco, has assembled a team of experts with deep experience scaling microbial fermentation and takes a different host approach, utilizing a proprietary industrial organism to produce a wide range of cannabinoids. Although still a young company, Purissima has already attracted investments from some of the early pioneers and investors in the industry who understand the value of its technology.

> *"Purissima transforms natural medicines into next generation household staples and high impact therapeutics, empowering brands and retailers with customized solutions built on unmatched purity, consistency and reliability."*
>
> Rob Evans,
> Co-founder of Purissima

BayMedica, based in San Francisco, aims to produce natural cannabinoids and novel cannabinoid analogs in their yeast production platform[41]. Yeast is the platform of choice for another cannabinoid-

[36] https://synbiobeta.com/amyris-finalizes-cannabinoid-development/
[37] https://www.bloomberg.com/news/articles/2018-09-04/cronos-partners-with-ginkgo-to-develop-lab-grown-cannabis
[38] https://synbiobeta.com/intrexon-announces-advances-in-production-of-medical-cannabis/
[39] https://synbiobeta.com/intrexon-corporation-and-surterra-wellness-partner-in-100mm-deal/
[40] https://www.theguardian.com/society/2018/oct/22/cannabis-from-yeast-synthetic-biology-cbd
[41] https://www.baymedica.com/cannabinoid-biosynthesis/

producing startup, **BioTork**, based in Florida[42]. **Teewinot Life Sciences**, also based in Florida, holds a Canadian patent on the biosynthesis and manufacturing of cannabinoids[43]. **Librede** and **CB Therapeutics**, both located in San Diego, work around lab-grown cannabinoids[44]. The Canadian biotech company **Willow Biosciences,** the first biosynthetic cannabinoid company to go public, is also moving into cannabinoid bioproduction, using its yeast-based production platform currently used for opioids[45]. **Octarine Bio** from Copenhagen, Denmark, aims to produce cannabinoids with improved properties in yeast too[46].

Farmako is a German biotech company that uses a different production host, the bacterium *Zymomonas mobilis,* which is also used for the production of tequila, was genetically modified in such a way that, in addition to CBD and THC, it can also produce 180 cannabinoids. This production method has the advantage that the cannabinoids will be excreted in the medium (while yeast will retain them in the cell), making production and harvesting less costly. "*With one production run, we can produce cannabinoids for 900 hours without interruption. For example, 4.5 kilograms of THC are produced per gram of bacterial mass during this tim*e, "explains Patrick Schmitt, co-founder of Farmako and Chief Science Officer of the company[47]. **InMed Pharmaceuticals** aims to use the traditional molecular biology workhorse, *Escherichia coli*, for bioproduction of cannabinoids[48].

Renew Biopharma, a San Diego-based synthetic biology company, uses microalgae as their production host[49]. **Algae-C**, an algae biosynthetic company also plans to achieve industrial-scale bioproduction by 2020. The company's founder, Dr Mather Carscallen notes that "*algae have already the right biosynthetic precursors abundant within them*", making them excellent potential hosts[50]. The third company aiming to use algae as microbial producers is **FSD Pharma** in collaboration with **Solarvest BioEnergy**, both from Vancouver, Canada[51].

Biotii Technologies, a Vancouver-based cannabinoid fermentation company, announced in April a 1.2 $ million investment in partnership with **International Cannabis Corp**[52], and plans to

[42] https://www.biospace.com/article/releases/-b-biotork-b-release-producing-cannabinoids-with-yeast-/
[43] https://synbiobeta.com/teewinot-life-sciences-grant-cannabinoid-formulations/
[44] https://techcrunch.com/2018/09/06/cb-therapeutics-lab-grown-cannabinoids-could-unlock-new-medicines-and-make-others-affordable/
[45] https://midasletter.com/2019/05/willow-biosciences-inc-cnsxwllw-ceo-explains-share-consolidation/
[46] https://bioinnovationinstitute.com/news/meet-the-start-ups-octarine-bio/
[47] https://synbiobeta.com/genetically-modified-tequila-bacterium-produces-cannabinoids-from-sugar/
[48] https://www.prnewswire.com/news-releases/inmed-pharmaceuticals-announces-transition-to-a-single-cannabinoid-investigational-drug-candidate---inm-755---for-its-epidermolysis-bullosa-program-300811410.html
[49] https://synbiobeta.com/renew-biopharma-launches-pre-clinical-drug-discovery/
[50] https://midasletter.com/2019/06/algae-c-beginning-commercial-growth-trials-this-summer/
[51] https://www.cannabisfn.com/fsd-pharma-looks-to-grow-cannabinoids-in-algae/
[52] https://synbiobeta.com/icc-makes-strategic-investment-in-disruptive-biosynthesis-research-cfn-media/

make one of the first automated high-throughput facilities for cannabinoid production with the use of **Opentrons**' robotic equipment[53].

It may not even be necessary to use a cell host to produce cannabinoids. Researchers from UCLA have shown that it is possible to produce the compounds using cell-free technology[54], and the UCLA spinout **Invizyne Technologies** aims to do just that in commercial scale.

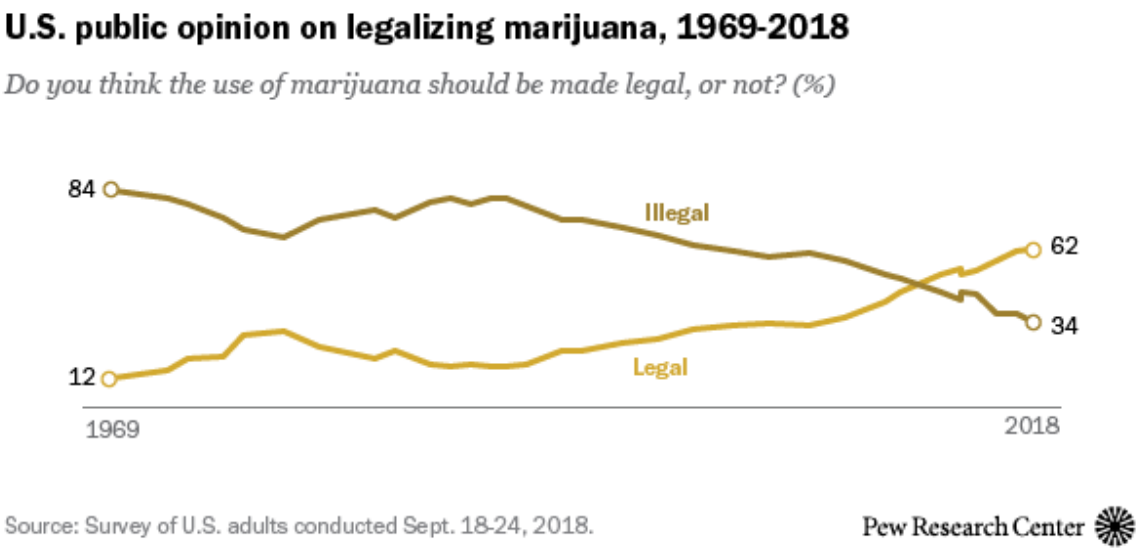
On the industrial "demand" side of cannabinoids, several large food producers have announced plans to enter the cannabinoid market. These examples in the beverage industry alone suggest that future demand for high-quality, low-cost cannabinoids will be great:

- Constellation Brands Inc., maker of Corona beer, has invested $3.8 billion in Canopy Growth
- Molson Coors Brewing Co. has started a joint venture with Quebec-based Hexo Corp. to sell nonalcoholic cannabis drinks
- Coca-Cola Co. has said it's interested in CBD-infused beverages, although it doesn't have immediate plans to enter the market

[53] https://synbiobeta.com/international-cannabis-biotii-and-y-combinator-backed-biotech-innovator-to-build-bioworks-foundry/

[54] https://www.theguardian.com/society/2018/oct/22/cannabis-from-yeast-synthetic-biology-cbd

10. Consumers, labeling, and bioengineered products



Current CBD users overwhelmingly view cannabis as a solution to a range of health and wellness challenges. About 40 percent of U.S. adults age 21 and over show a willingness to explore CBD under the right conditions. 79 percent of potential users have college experience, and 64 percent are 35+ years old. Baked goods and chocolates are the products with the highest interest level, which may have implications for how manufacturers select cannabinoid compounds with specific properties.

> *"We're noticing CBD companies are manufacturing new and creative products offering diverse ways ingest CBD. We see new skincare products, edibles, CBD tinctures mixed with supplements, and more. This allows them to capture a wider audience."*
>
> Cyrus Partow, CBDNerds

Fermented cannabinoids are made using genetically engineered microbes, but the cannabinoid ingredients produced are themselves equivalent to plant-based products. As such, fermented cannabinoid products may be labeled "non-GMO", although they may not be labeled "organic" since the products of biosynthesis do not apply to this designation.

A recent SynBioBeta study shows that consumers often conflate organic with non-GMO labels, and that high-income, liberal, and educated consumers are most likely to have an anti-GMO

bias[55]. It remains to be seen whether the inability to label products as organic will be an impediment to the fermented cannabinoids market, or if it represents an opportunity to create a new consumer enthusiast segment about the improved performance of products made with biotechnology.

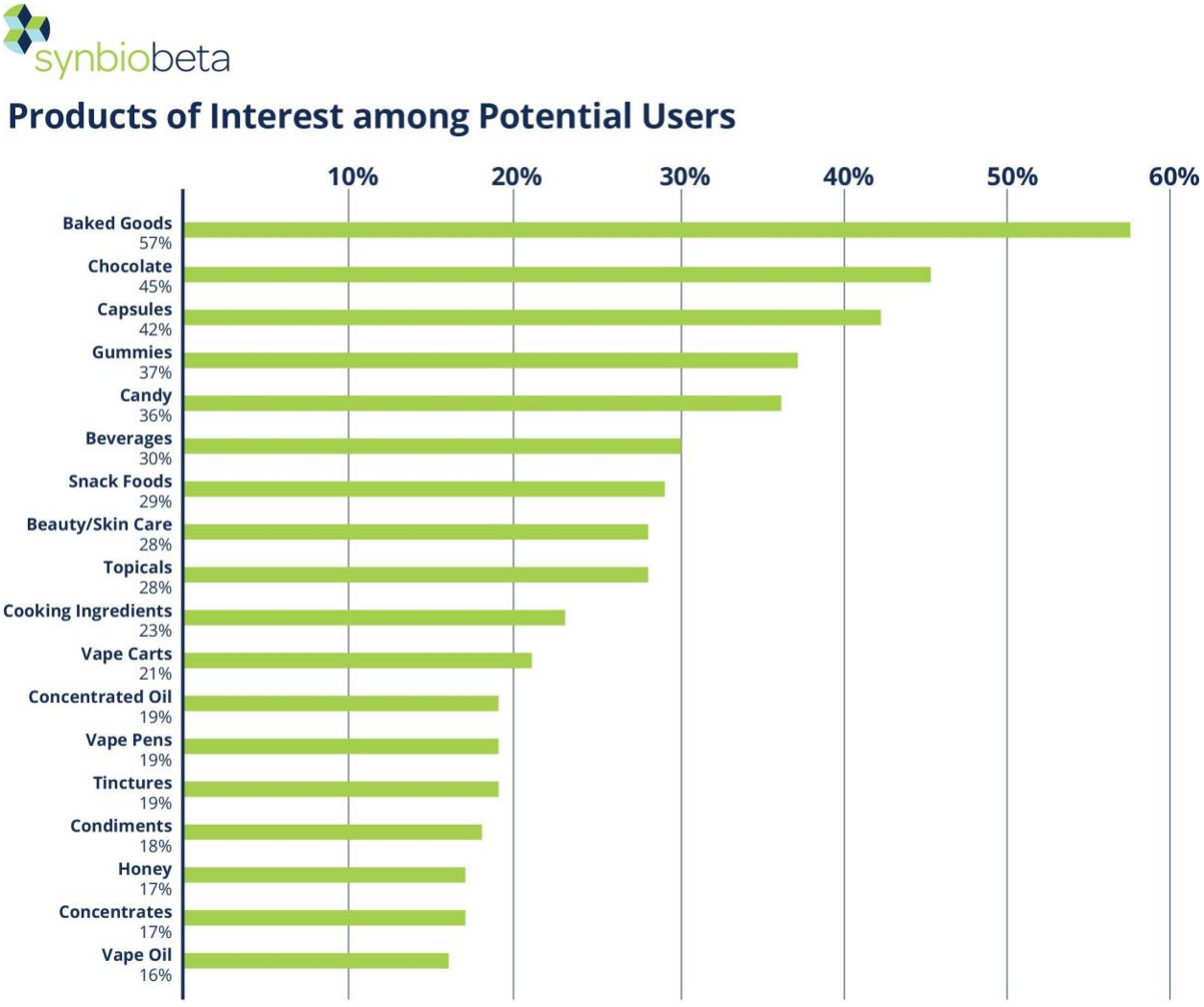


Figure 5: Consumer CBD products of interest. Adapted from [High Yield Report](#).

[55] https://synbiobeta.com/synthetic-biology-industry-strategy-reports/how-do-you-decide-about-gm-foods/

Regarding safety and efficacy, the HighYield Insights survey reveals that **only 34% of current cannabinoid users are confident in the safety of CBD products**[56]. More strikingly, only 16% of current users are confident in the accuracy of the potency or concentration on product labels. Fermented cannabinoid products present an opportunity to market more reliable consumer labeling in terms of potency and composition of specific cannabinoid compounds. Product marketers could also highlight the fact that fermented cannabinoids do not introduce a chemical solvent purification step, representing a safer and purer product that is free from toxic substances.

Examples of consumer needs in cannabinoid labeling include[57]:

1. Cannabinoid sourcing and processing (hemp, organic, extraction methods used)
2. Full spectrum versus isolate composition: A single cannabinoid such as CBD or THC, or a combination.
3. Third-party lab results on potency and purity
4. Dosage and delivery methods

[56] https://www.highyieldinsights.com/products/cbd
[57] https://cbdnerds.com/

12. Conclusions

> *"The cannabinoid fermentation industry has gone from zero to one, and synthetic biology is doing what it does best: Making the picks and shovels that disrupt conventional industry."*
>
> John Cumbers, Founder and CEO of SynBioBeta

Using the tools of synthetic biology, innovators are making a bold move into the cannabinoid industry, particularly as cannabinoids are increasingly recognized for their therapeutic uses. Cannabinoid fermentation is more precise, economically scalable, and environmentally sustainable than plant production. Biotechnologists are supported by a growing list of investors who recognize tremendous consumer interest and an improving regulatory landscape. Cannabinoid fermentation is poised to become a major future supplier of high-grade, low-cost cannabinoids for therapeutic research purposes, as well as a booming consumer market.

Nonetheless, a few factors call for caution. First and foremost, the legal and regulatory landscape remains uncertain. Second, even though fermentation itself is very mature, it will take some time -- not just months, but one or more years -- before biosynthetic routes are optimized and fermented cannabinoids are commercialized, and longer still before it is highly economical. And third, the cannabinoid ecosystem (for both traditional extraction and biosynthesis) is becoming crowded, meaning there will likely be some consolidation and losers among this first batch of innovators.

Synthetic biology promises to significantly shape the emerging cannabinoids industry from the ground-up by providing low-cost, high-quality active ingredients. It will enable a broad range of therapeutics and products for patients and consumers, and give them improved labeling and decision-making ability. The next couple of years are likely to establish the leading innovators, producers, and investors in cannabinoids for many years to come.