The Holy Grails of Cannabis

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That's right, there's more than one. With more research being conducted on cannabis, it's becoming clearer that there is a lot more to find. It's safe to say that most people in the industry are familiar with delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD). The substances stand as the main commodities traded through today's cannabis and hemp derivative market. From a medicinal standpoint, these two cannabinoids have demonstrated effectiveness in treatments for multiple sclerosis [1,2], muscle spasm/seizure [3, 4], chronic pain [5], certain neuropathic disorders [6], and there's even data showing potential cancer-fighting properties [7]. THC is iconic for the psychoactive "high" associated with human consumption. CBD is non-psychoactive and favored for its therapeutic roles. But why is the modern understanding and mainstream use of cannabinoids limited to just two?

Despite the growing wealth of information regarding cannabis as a whole, there is very little awareness about the defining class of molecules within cannabis. There are more than 100 other cannabinoids, so it's possible that THC and CBD are just the tip of the iceberg. Any of the numerous discovered, or yet, undiscovered cannabinoids, could serve in treatments currently outside the known spectrum. Statistically speaking, the odds are *in our favor. There just needs to be* more research done on bringing these untapped resources into the public eye.

Lesser-known, or minor, cannabinoids exist because the precursor enzymes in cannabis that create parent cannabinoids, such as cannabigerolic acid (CBGA), aren't perfect. Due to frequent variation, these enzymes are called "promiscuous enzymes." The term is appropriate, considering that they often connect to molecules that don't fit perfectly, rather than waiting to bind with a specific one. After one of these, potentially randomized, molecules is chosen, the enzyme attempts to build a cannabinoid with it. Here, it's possible to end up with different families of cannabinoids that resemble each other, but have lots of isomeric variation. It's important for non-chemists to note that the smallest molecular difference can yield vastly different pharmacological effects. The easy example here is THC and CBD. There's only a minute difference between their molecular structure, yet they exhibit vastly different properties.

As a community, one of our central objectives is to isolate minor cannabinoids. The goal is to push these through legitimate medical trials, from which re-producible data is generated. With that, the findings can be made public. The process begins with creating isolates. Fortunately, there are multiple ways to isolate minor cannabinoids:

1. Early Harvest of Low Hanging Fruit: Harvesting early will yield small flower plants with small trichomes *rich in CBGA and cannabichromenic* acid (CBCA). These are the initial cannabinoids produced in the plant's lifecycle, and both can be extracted. Or, if those extracts are not pure enough, a simple column can be run to raise concentrations enough to crystallize out desired cannabinoids.

2. Post-Processing Methods for Reduced or Oxidized Cannabinoids: A decently equipped laboratory can produce cannabinol (CBN), cannabicyclol (CBL), and/or cannabitriol (CBT) quite easily using ultra-violet degradation and/or heat to facilitate reduction or oxidation, depending on the desired end-product. Gaining access to THC, CBD, and CBC in the modern world is a relatively simple process.

3. Column Chromatography: This involves separating minor cannabinoids from cannabis or hemp using normal or reverse-phase column chromatography. Procedurally, this method takes advantage of the polarity differences between cannabinoids to create pure isolations. Very common in the pharmaceutical world for performing separations, it is often combined with other purification processes if higher quality final products are desired. The cost of this method is traditionally high, making it difficult to scale relative to the available genetics on the market. Costs and scalability, of course, depend upon the molecule of interest. Ideally, a cannabinoid would be chosen for separation that exists at, around, or above, a 1% concentration in dried flower.

4. *Column Chromatography Combined* with Selective Breeding: GW Pharmaceuticals has already bred plants to produce singular terpenes and Green House Seed Co. has ventured the world to find Congo genetics high in

tetrahydrocannabivarinic acid (THCVA). Selectively breeding cannabis to boost production of the minor cannabinoids is a fantastic way to sustainably scale. This has the added benefit of reducing the costs associated with isolating new cannabinoids of interest. These reasons make this model the most scalable for the recreational market.

5. Genetic Modification: A controversial topic is using genetic modification to maximize desired growth. With GMO assisted selective breeding, the use of invasive techniques will undoubtedly boost desired cannabinoid production. Cannabis can then be modified at the genetic level to increase certain enzymes while decreasing others. The handicap here is that this route requires a significantly developed level of biochemistry expertise. On the other hand, a shortcut appears in the opportunity to genetically modify yeast to produce the desired cannabinoids. This would allow for the mass production of cannabinoids in tanks (similar to insulin production). From a procedural perspective, this process requires minimal post processing to achieve high purity.

A few readers may be triggered that genetic modification techniques were included. However, regardless of ethical positioning, some thought could be given to the idea. It's also notable that large pharmaceutical companies are integrating with the cannabis industry. This means that they're trying to isolate these minor cannabinoids, too. If they manage to produce their own medical trials and receive FDA approval before the traditional cannabis community, then those companies can create a monopoly on those cannabinoids. However, this can be prevented if local universities with cannabis research facilities, like UCLA and UCSD, receive support. Everyone deserves to have access to the medical benefits of cannabis, even if those applications haven't been discovered yet.

References

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