Cannabidiol (CBD) has been highly touted and heavily hyped. Its medicinal qualities are perceived as limitless by some, and its non-psychoactive nature makes it suitable for just about anyone—or so it has been claimed. Entrepreneurs are jumping in on CBD as rapidly and in abundance. CBD has been sold as oil, in capsules and syrups, in topical lotions and creams, and as an additive in food products or beverages, all in over-the-counter form.

Unfortunately, peer-reviewed clinical research into the true therapeutic and healing qualities of CBD has been severely limited. Cannabis research, in general, has been repressed as a consequence of the drug being listed under the federal government's Controlled Substances Act, where it remains under Schedule I status.

While the Drug Enforcement Agency (DEA) hasn't changed its anti-cannabis stance, other government agencies have been more open-minded. Both the National Institutes of Health (NIH) and the U.S. Food and Drug Administration have taken a role in supporting or approving further research into the medicinal effects of CBD and other cannabinoids.

Scientific research must be unbiased, which means uncovering the benefits, as well as revealing any potentially *adverse*effects caused by long-term use or extremely high doses. Anything in excess can be harmful, so the idea is to discover the limits of cannabinoid supplementation and therapies.

Researchers at Kannalife and GW Pharmaceuticals are working to find those answers.

CBD and Liver Toxicity

In 2018, GW Pharmaceuticals received approval from the FDA to begin marketing its anti-seizure drug Epidiolex, which is a form of CBD used to treat some cases of severe childhood epilepsy. To gain approval for Epidiolex, GW Pharmaceuticals had to sponsor clinical trials to demonstrate its efficacy. They succeeded in doing just that, but some alarming results were also obtained during these evaluation procedures.

"When they actually went and tested it in a clinical trial, they found a number of toxicities that were of significant concern," explains Dr. Douglas Brenneman, a medical researcher employed by Kannalife Sciences, Inc., a biotech firm involved in the search for CBD-based medicines. "The number one concern is liver toxicity."

Elevated levels of certain enzyme levels associated with livers in distress tipped researchers off to the problem. One of these enzymes, called transaminases, was found in excessive amounts in 15 percent of the patients involved in the clinical trial.

More concerns were raised about the potential for CBD to harm developing organisms, including human fetuses. There is also uncertainty about how CBD might interact with other medicines and the harmful physiological responses that might be provoked by such combinations.

The results of the testing on Epidiolex may have caught some people by surprise. But researchers at Kannalife already knew there were problems, based on their internal evaluations.

“We were early to identify possible developmental toxicity issues from long-term use,” says Kannalife founder and CEO Dean Petkanas. “We were also able to point out in our preclinical work that there were liver toxicity issues, potentially. When we saw the limitations, we said ‘well, maybe we can endeavor to make CBD better.’”

Kannalife has focused on creating CBD analogs to treat neurodegenerative disorders. Its most promising synthetic candidate at the moment is KLS-13019, which is designed to treat neuropathic pain.

“Now we have a potent neuroprotective molecule,” says Dr. Brenneman, who is Kannalife’s lead biochemical researcher. “We’re getting some understanding of properties; it can elicit that CBD cannot.”

The potential liver toxicity of KLS-13019, and other such compounds, remains a concern. As of yet, Kannalife’s research on the drug has not been able to quantify the exact level of risk this medicine might create, and at what doses. It cannot say, for example, if the risk of liver damage is lesser or greater than that associated with prolonged use of the painkillers acetaminophen and ibuprofen, which carry FDA warning labels but are still available in over-the-counter formulations.

The FDA Cracks Down

Some companies marketing products containing CBD have been over-exuberant in their claims about its effectiveness. They have been guilty of some clever (and illegal) sleight-of-hand, exploiting public enthusiasm over cannabis by portraying all cannabis compounds as not only safe but capable of ameliorating the symptoms of many serious medical conditions.

"In the world of commerce, if you can get into the marketplace without federal regulation or oversight, you do it," Petkanas explains. With the trade in cannabis-related "health" products growing by leaps and bounds, however, it was only a matter of time before government authorities took notice.

In November 2019, the U.S. Food and Drug Administration took action to crack down on some of the more egregious violators. It issued warning letters to 15 companies, telling some of them to cease and desist making unproven and extravagant claims about the capacity of CBD to cure or prevent disease. Other companies were tagged for selling CBD as a dietary supplement, while others were guilty of illegally adding CBD to human and animal foods.

To justify its actions, the FDA pointed to studies that have revealed potentially dangerous side effects that may be experienced by at least some users of CBD. The FDA issued a revised Consumer Update detailing some of these side effects, with the risk of liver injury mentioned prominently. The report emphasized that research on the impact of long-term cannabinoid use, and into the effects of CBD on developing fetuses, was too sparse to ease concerns.

"It's a bit of a conundrum for the marketplace," says Petkanas. "The tail got busy wagging the dog for the last couple of years. Now we're starting to see the market cool off a little bit for these over-the-counter products, and the FDA is taking a more active role in how they're going to treat CBD going forward."

Kannalife Partners with the NIH

While research into the benefits of CBD has been relatively scarce, what has been carried out has produced some impressive results—impressive enough that the National Institutes of Health sought and received a medical patent on CBD in 2003, giving it the right to sponsor further research into the compound's health-restoring and preserving capacities.

In their application for the patent, the NIH noted that some non-psychoactive cannabinoids "are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic results, such as stroke or trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and HIV dementia."

The NIH patent on synthetic and natural non-psychoactive cannabinoids, with CBD being perhaps the most notable, didn't put the federal government in the cannabis business. But it did open the door for increased research into the possible medical benefits of cannabinoids, and Kannalife was only too happy to take advantage of this development.

Kannalife Sciences, Inc. signed an exclusive licensing agreement with the NIH Office of Technology Transfer in 2012. This agreement permitted the firm to pursue research into the effectiveness of CBD as a neuroprotectant, individually as an antidote to hepatic encephalopathy (HE), a degenerative brain disease linked to liver failure, and chemotherapy-induced peripheral neuropathy (CIPN), a chronic and painful nerve condition caused by the toxic effects of chemotherapy. In 2018, Kannalife was awarded a Phase 1 study grant from the National Institutes of Health – National Institute on Drug Abuse (NIH-NIDA) to study the effects of KLS-13019 on the treatment of CIPN.

In February 2020, Kannalife announced results from that study, which compared '019 [KLS-13019] to CBD and Morphine in the CIPN model. The study was conducted by Kannalife's neuro-pharmacologist and lead scientist, Douglas Brenneman, and Dr. Sara Jane Ward, Ph.D., an Assistant Professor of Pharmacology at the Lewis Katz School of Medicine at Temple University. In commentary by Dr. Ward regarding the results, she stated, "In our model, KLS-13019 is at least as effective as CBD to prevent neuropathic pain; however, KLS-13019 is also effective to reverse neuropathic pain as a consequence of cancer chemotherapy, whereas CBD was not effective under our test conditions."

Kannalife's steady approach to validating the use of cannabinoid-based treatments in an ethical pharmaceutical model has paid off for GW Pharmaceuticals in their drug Epidiolex Ò and Kannalife believes its efforts to produce advancements through its novel CBD analogs will eventually do the same.

Pursuing an exhaustive and meticulous approach to research and development, Kannalife has been progressing steadily, working toward a future where its synthetic CBD compounds are accepted by the medical establishment and routinely prescribed for the appropriate conditions.

There are, of course, added costs associated with such an approach. As determined by FDA rules and protocols, it can take several years for a new compound to pass through various testing stages before it is declared ready to hit the market.

But from the standpoint of consumers, CBD-based products that follow this path will carry a medical imprimatur that should guarantee quality, reliability, and safety. If and when Kannalife's KLS-13019 becomes available via prescription, it will come with dosage and duration-of-consumption recommendations that should prevent deleterious effects in most cases.

CBD is Worth the Wait

Under the current regulatory structure, before the FDA approves any CBD-based medicine, it must be verified as safe in preclinical research and clinical trials. Potential risks must be weighed against potential benefits, and the final decision must be made based on the results of these calculations. FDA approval doesn't guarantee the complete absence of side effects in users, but it does signify the capacity of a drug to help most patients who take it as prescribed.

Unlike some other companies looking for the pot of gold at the end of the CBD rainbow, Kannalife has signaled its intentions to stay patient and proceed responsibly. It will follow all standard research protocols and only release and market its medicines when they have been approved, and the company itself is confident of their efficacy.

This is the most sustainable approach for cannabis producers and manufacturers in the long run. It is an approach that will allow CBD and its analogs to prove their worth as potent, versatile, and safe medicinal remedies for a variety of disorders and conditions.