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Natural vs. Novel Cannabinoids

Alec Anderson and Jillian Thayer

Abstract
Cannabis has been cultivated and used for millennia by the human race. The original medicinal and industrial uses of cannabis were almost forgotten during the vilification during the early 20th century. However, with renewed focus, interest, and tolerance, this species has found itself in the limelight of its original purpose. Cannabinoids have become a staple in modern holistic medicine and have even found mainstream medicinal applications. Confusion has arisen over the classification of its primary compounds, cannabinoids, as well as to the presence of similar compounds in other plant species. Novel cannabinoids produced legitimately by researchers or illicitly by clandestine chemists have only added to this issue and furthered the need for unification not only in understanding, but also in terminology. This review seeks to define critical terms for cannabinoid chemistry as well provide an introduction to the variety of compounds.

Keywords: Cannabinoids, Cannabis plant, novel cannabinoids, cannabinoid receptors

1. Introduction
For hundreds of years the medicinal and industrial properties of the cannabis plant have been known throughout the world. Its physical properties make it a versatile fiber, an alternative paper source, and even as a construction material [1]. Many of the medicinal and recreational properties can be attributed to compounds produced by the cannabis plant called Cannabinoids.

Over 120 natural cannabinoids have been identified in the cannabis plant with new compounds being discovered regularly [2]. Additionally, there have been reports of other chemicals that interact with the endocannabinoid system in similar ways that cannabis derived cannabinoids do [3]. This has created confusion among the scientific and consumer communities. The term "cannabinoid" has evolved from its original meaning since it's coining in 1968; it no longer refers exclusively to cannabis derived compounds, but now to any compound that interacts with the endocannabinoid system receptors. "Cannabinoid" can be used as an umbrella term to describe a wide variety of compounds that all interact with the endocannabinoid system, both directly and indirectly. Indirectly interacting compounds are known as "cannabimimetics," meaning they can mimic the effects of cannabinoids, but do not interact directly with the cannabinoid (CB) receptors in the nervous system. Any cannabinoid, direct or cannabimimetic, can be described as cannabinoidergic, meaning "working on cannabinoid neurotransmitters."

2. Cannabinoid Classification
Cannabinoids can be broken down into three broad categories: Phytocannabinoids (plant derived), Endogenous (produced in the body), and Synthetic (created in a lab).

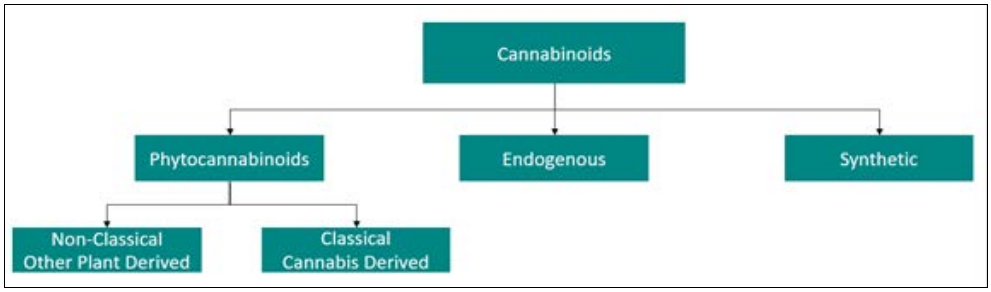

Fig 1: Cannabinoid Classifications

Phytocannabinoids can be broken down even further, Classical (the original cannabinoids discovered in cannabis, giving the class of compounds its namesake) and non-Classical (compounds discovered in plants other than cannabis). Classical Cannabinoids can be further divided to groups based on their precursor compounds.

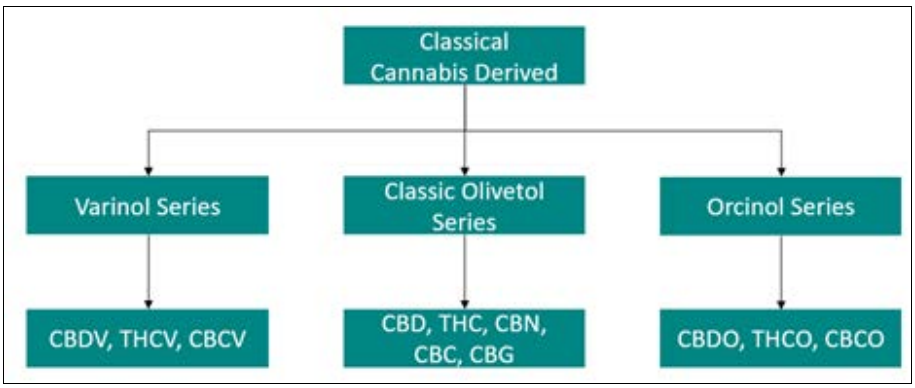

Fig 2: Classical Cannabinoid Classifications

Non-classical compounds are categorized by class, to name a few, Fatty acid derivatives, Terpenes, Polyphenols, and Bibenzyls.

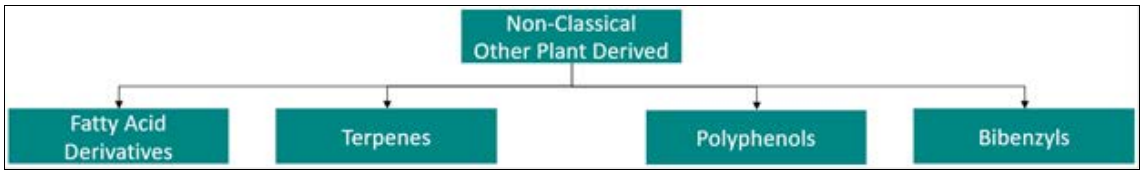

Fig 3: Non-Classical Cannabinoid Classifications

2.1 Classical Phytocannabinoids

The most widely studies phytocannabinoids are Δ9-Tetrahydrocannabinol (THC), Cannabinol (CBN), and Cannabidiol (CBD). All three of these have similar moieties. Additionally, these all can be considered Olivetolic cannabinoids, meaning they all use Olivetol as a building block.

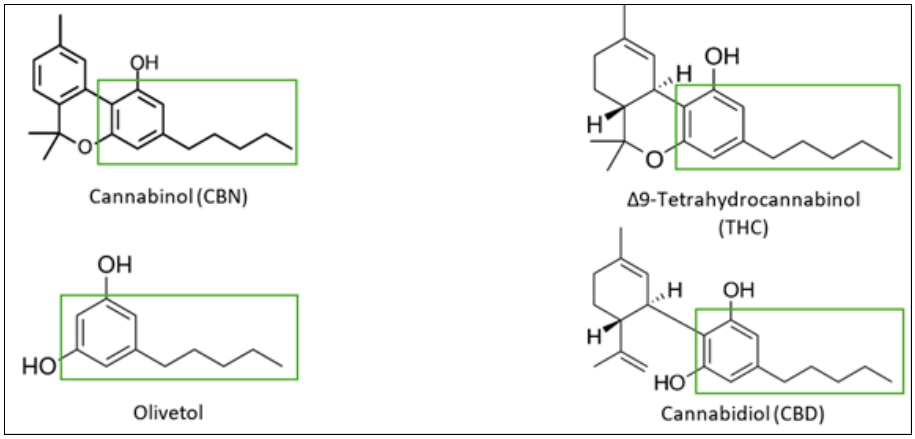

Fig 4: Olivetolic cannabinoids with base olivetol

All three of these cannabinoids can bind to human CB_2 receptors in the nervous system [4]. The other two major classes of classical cannabinoids (Orcinol and Varinol) are nearly identical to their Olivetolic cousins, the only difference being in the side chain length.

2.2 Fatty Acid Cannabinoids

Fatty acid cannabinoids can be either true cannabinoids or cannabimimetics. *N*-acylethanolamines (NAEs), which can be isolated from a variety of plants, are cannabimimetic, they do not interact with CB receptors. Rather, they inhibit other types of receptors which can in turn lead to modulations in the endocannabinoid system [3]. Other cannabimimetic compounds have been found in chocolate, *N*-linoleoylethanolamide and *N*-oleoylethanolamide have been shown to inhibit the breakdown of anandamide, an endogenous cannabinoid [5].

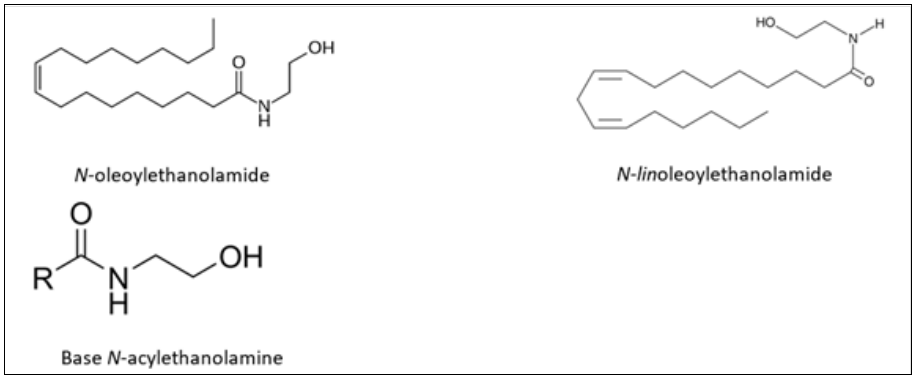

Fig 5: Fatty acid cannabinoids

Directly interacting fatty acid cannabinoids can be found in Echinacea. Certain *N*-alkylamides have been found to interact with human CB_2 receptors at low concentrations [6].

2.3 Polyphenols

There has been confusion in regard to the effects of *trans*-resveratrol (a compound produced by a variety of plants in response to trauma [7] and curcumin (found in turmeric) on the endocannabinoid system. In one study, the two compounds were shown to have a direct and potent effect on cannabinoid receptors [8], however, a separate study could not reproduce those results [3].

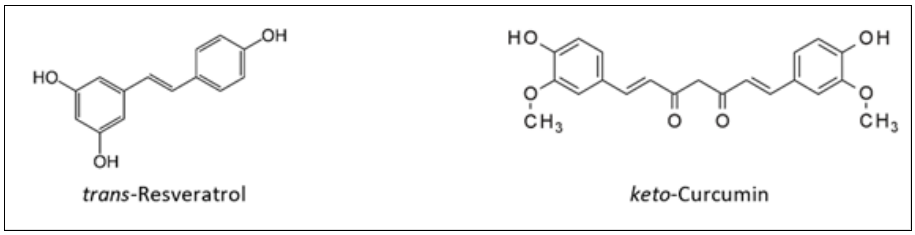

Fig 6: Investigative polyphenolic cannabinoids

A number of catechins, found in tea, as well as certain plant pigments (Cyanidin and Delphinidin) have been observed to directly bind to cannabinoid receptors [9, 10], albeit at very high levels. This high-level binding affinity may be the result of nonspecific denaturation of the proteins rather than functional binding. This leads to the conclusion that the binding proteins were being destroyed by the compounds rather than being used. An explanation of these findings is that both studies were conducted *in vitro*, Latin for "in glass" meaning these tests were conducted only in the lab, and not in a live model or *in vivo* "in the living." During an *in vivo* experiment, the compounds would likely be administered orally or intravenously ensuring they would be metabolized. This would only allow for small portions (or perhaps none, depending on the chemical) to reach the cannabinoid receptors. Conversely, during an *in vitro* study, the compounds can be directly applied to the binding proteins, circumventing the metabolic and blood-brain barrier roadblocks.

Indirect, cannabimimetic polyphenol compounds have also been observed. Genistein (*Genista tinctorial*), Kaempferol (kale, tea, broccoli), 7-hydroxyflavone, and 3, 7-dihydroxyflavone have all been observed to indirectly inhibit the breakdown of anandamide [11, 12] in rat brains, producing the same effect as certain fatty acid cannabimimetics.

2.4 Terpenes

Research into the effect of terpenes on the endocannabinoid system has been volatile to say the least. Researchers began to discuss the idea of an "entourage effect" in cannabinoid chemistry. The entourage effect is a proposed theory that, although cannabinoids can interact with the endocannabinoid system a la carte, they produce greater results while accompanied by an "entourage" of other chemicals present in cannabis plants [13]. Terpenes have been a major focus of this theory in recent years, with many papers supporting or refuting the claims of the theory.

Researchers have suggested that papers purporting to have disproved a terpene's status as a cannabinoid (direct or cannabimimetic) [14] have only used low concentrations of the terpenes, and that when concentrations of terpenes are increased, direct interaction can be observed [15].

One terpene that most researchers can agree is most certainly a directly acting cannabinoid is the sesquiterpene β-caryophyllene. β-caryophyllene is a major constituent of the essential oils of rosemary, hops, clove, and interestingly enough, cannabis. β-caryophyllene has been shown to be a selectively target CB_2 receptors at very low concentrations [16].

Other terpenes that can be found in the cannabis plant, in addition to others, that are currently being studied for cannabinoidergic activity include but are not limited to linalool, α-humulene, β-pinene, and geraniol.

Beyond the cannabis plant, a terpenoid and moderate hallucinogen isolated from *Salvia divinorum*, Salvinorin A, has been reported to be both an opioid and cannabinoid agonist under certain conditions [17]. Two frequently occurring triterpenoids, Pristimerin and Euphol were found to be cannabimimetic in mice [18].

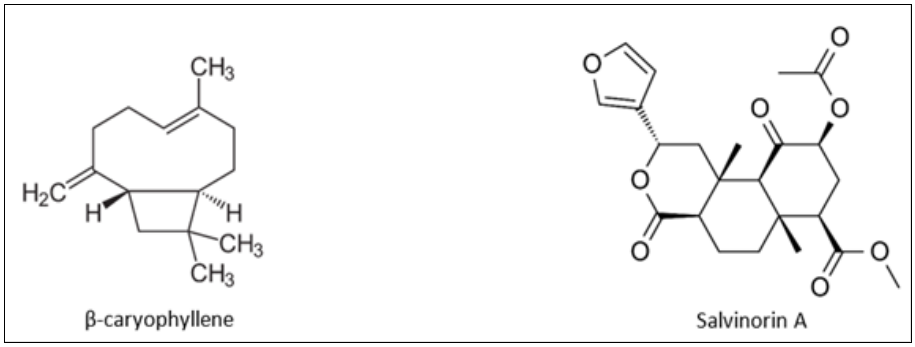

Fig 7: Terpene cannabinoids

2.5 Bibenzyl Derivatives

Certain compounds have been isolated from a number of non-cannabis species that possess a striking similarity to classical cannabinoids both in function and in structure. A report published in 1979 by Bohlmann and Hoffmann documented the presence of both CBG (1A in Fig. 8) and CBGA in *Helichrysum umbraculigerum* from South Africa [19]. However, an attempt to validate those reports in 2017 did not detect any CBG or CBGA in *Helichrysum umbraculigerum*. They did, although find a number of bibenzyl derivatives of CBG [20] some of which were reported originally by Bohlmann, others had not been seen before. During testing, this newly termed Heli-CBG (2a in Fig. 8) performed comparatively to classical CBG in receptor binding studies [20].

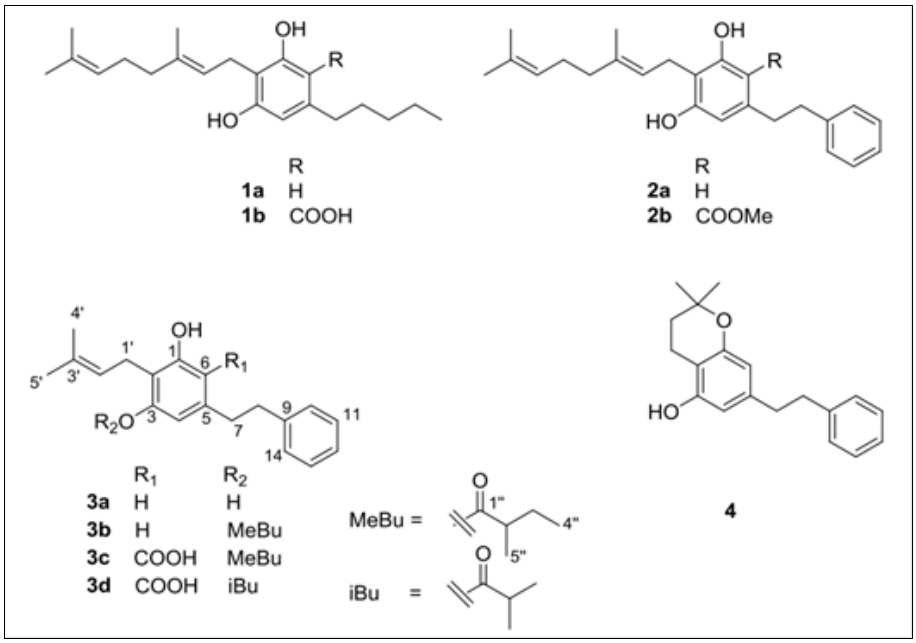

Fig 8: Numerous bibenzyl cannabinoids found in *H. umbraculigerum*

A THC bibenzyl analog was discovered in species of liverwort endemic to New Zealand in 2002 [21] along with other bibenzyl cannabinoids. The cannabinoid known as Perrottetinene is the most widely studied compound identified from the study and has since demonstrated moderate psychoactivity and cannabinoid binding ability [22].

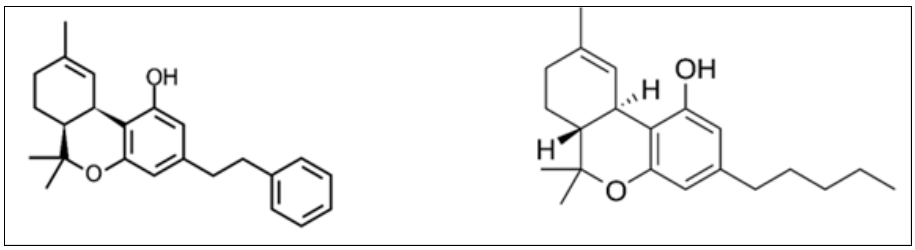

Fig 9: Perrottetinene (left) compared to Δ9-THC (right)

The discovery of these analogues has highlighted the remarkable co-evolution between plant species to develop cannabinoids independently from one another using different biosynthetic pathways [23]. Numerous other plants have shown to produce directly and cannabimimetic compounds that are either weakly binding/interacting or poorly understood. The search for non-classical cannabinoids as well as undiscovered classical cannabinoids is still ongoing and likely will be for the foreseeable future.

3. Synthetic Cannabinoids

The term "Synthetic Cannabinoids" can be confusing at times. It can refer to both synthetically produced cannabinoids that are found in nature, as well as man-made compounds that have never appeared naturally on Earth (to our knowledge) before their creation in the lab.

Synthetic THC is already produced in large quantities by pharmaceutical companies under the generic name Dronabinol. Dronabinol is used frequently as an appetite stimulant and antiemetic, most often prescribed to patients with AIDS and cancer patients undergoing chemotherapy [24].

Currently there are no synthetic CBD drugs on the market, as it is still considered a Schedule I drug by the DEA [25] (Dronabinol specifically was allowed be schedule III, however cannabinoids in general are still highly controlled by the federal government) [26].

Apart from synthetically produced natural cannabinoids, on the other side of the spectrum are the cannabinoids first synthesized in labs. The term "Synthetic Cannabinoids" has become synonymous with these lab-created compounds, and is typically used when describing them, although in reality the proper term would be Novel Cannabinoids (NCs).

Some of the first NCs were synthesized in the early 1970s by pharmaceutical companies, including Pfizer [27], in an attempt to create analgesics, sedatives, antiemetics, etc. without the psychoactive properties of natural cannabinoids. NCs created by Pfizer are denoted by the prefix "CP."

After the initial fruitless ventures, a golden age of novel cannabinoid synthesis took place in the 1980s and 90s. Three major groups arose during this period, in addition to Pfizer continuing their research from the 1970s.

John W. Huffman at Clemson university created hundreds of compounds, including the very first identified NCs in recreational substances in 2008 [28]. Compounds synthesized by his group at Clemson are denoted by the prefix "JWH."

Researchers lead by Raphael Mechoulam at Hebrew University created a number of compounds reminiscent of THC. These compounds are identified with the prefix "HU."

The last prominent group was led by Alexandros Makriyannis at Northeastern University. The group synthesized a variety of compounds, some resembling traditional cannabinoids in structure, others endogenous cannabinoids like anandamide, while others bared no resemblance to any known cannabinoid before it. These compounds are denoted with the prefix "AM."

NCs can be generally divided into 5 major classifications: Classical, Non-Classical, Hybrids, Aminoalklindoles, and Eicosanoids.

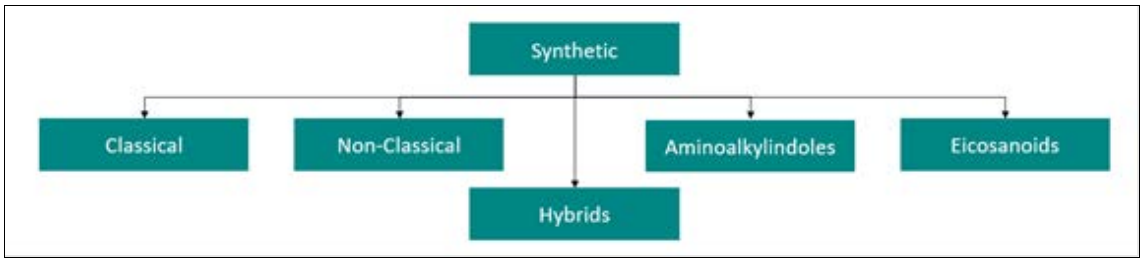

Fig 10: Synthetic Cannabinoid Classifications

The development and discovery of these compounds was carried out with the intent of developing pharmacological probes for use as investigative substances into the nature of the elusive (at the time) endocannabinoid system [29]. Apart from the theoretical application, practical aspects of these compounds were explored as well. Promising fields of application included treatments for inflammatory diseases and pain resulting from cancer [30].

Early NCs shared structural similarities to classical cannabinoids, namely THC. One of the first NCs was CP 55,940 developed by Pfizer in 1974. The compound shares a vaguely similar structure to THC, specifically the side chain attached to a benzene ring (Figure 11, green circle). This compound was found to be around 45 times more potent than THC [31].

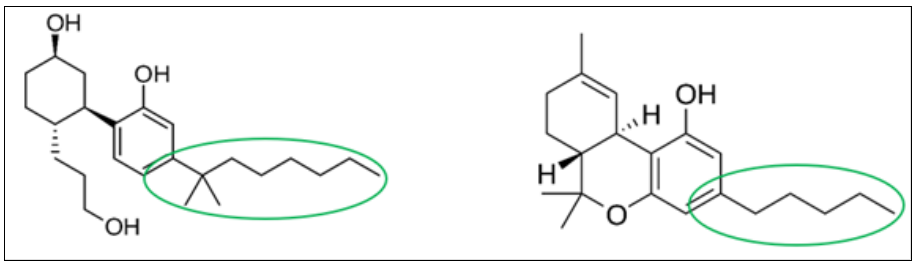

Fig 11: CP 55,940 (left) compared to Δ9-THC (right)

Though initially intended for clinical and research aspects, NCs have found their place in recreational and illicit use. Recreational uses of these compounds came in the early 2000s, with NCs being sold under the pseudonyms Synthetic Marijuana, Spice, and Incense. One of the first identified NCs being used in such products was JWH-018.

JWH-018 has 4-10x more binding capability than THC [32] and can produce effects for approximately 1-2 hrs [33]. Recreational use was somewhat widespread in Germany and Austria until it was banned in late 2008, early 2009.

A notable problem with NCs, as well as other designer drugs, is the ability for manufacturers to easily circumvent bans. One common practice is to simply alter a single functional group of a banned compound, thereby creating a new compound that is not subject to any legislation. After the ban of JWH-018, manufacturers shortened the alkyl side chain by one carbon (Figure 11, red arrow), producing a new compound (JWH-073) that was different enough to be "legal" [34].

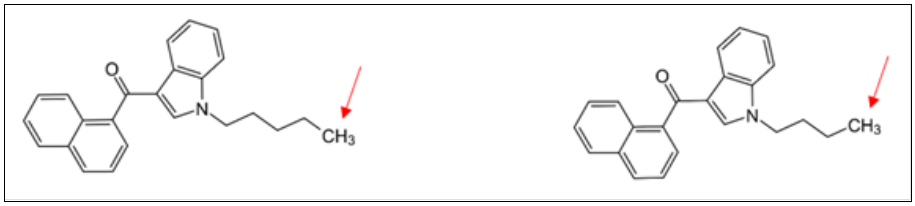

Fig 12: JWH-018 (left) compared to JW-073 (right)

This has created an extremely precarious situation for law enforcement groups. NCs have embodied the mythical hydra; after one compound has been identified and banned, three more analogues take its place.

Manufacturers of these substances also help to cover the liability of their product by labeling their packages as "not intended for human consumption." This simple statement keeps their companies at a safe distance from regulators and standards that would likely keep their products out of the hands of consumers.

3.1 Classical Synthetics

This group of synthetics is the blurred line between novel and phyto cannabinoids. The synthetic preparation of Δ9-THC, Dronabinol, is included in this category, as well as any other synthetic preparations of classical phytocannabinoids. On the other hand, novel cannabinoids that bear striking similarity to phytocannabinoids are also considered classical synthetics. Examples of classical novel synthetics include Nabilone, a novel cannabinoid pharmaceutical used in the same manner as dronabinol, and HU-210, a novel cannabinoid whose (-) enantiomer has shown promise as a promoter of neural growth resulting in anxiolytic and antidepressant effects [35].

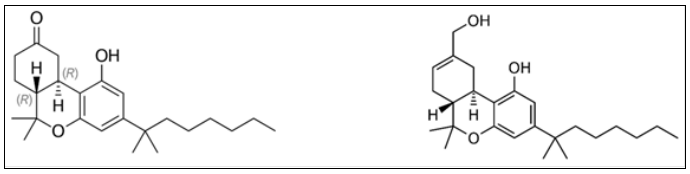

Fig 13: (R, R)-(-)-nabilone (left) compared to HU-210 (right)

Classical synthetic cannabinoids are not typically found in the illicit market, as they are difficult to synthesize [36].

3.2 Non-Classical Synthetics

The largest component of the Non-Classical Synthetic group are compounds known as cyclohexylphenols. These compounds were heavily developed by Pfizer in the 1970s and 1980s and include CP-47,497 and its homologue CP-47,497-C8 which has an extended side chain. These compounds were originally developed with the potential use as analgesics. The C8 homologue was one of the first compounds discovered in recreational products.

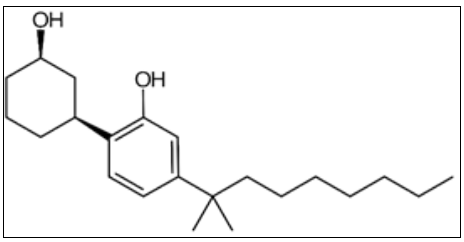

Fig 14: CP-47,497-C8

These cyclohexylphenol cannabinoids have been shown *in vitro* to increase inflammation responses and down-regulated proteins associated with DNA repair, implying they could be carcinogenic, although *in vivo* testing would be required to validate that claim [37].

3.3 Hybrids

Novel cannabinoids that share structural features of both Classical and Non-Classical NCs are considered Hybrid NCs. Most Hybrid NCs were developed by Alexandros Makriyannis at Northeastern University in Boston. Notable examples of Hybrid NCs are AM-919, AM-938, and AM-4030.

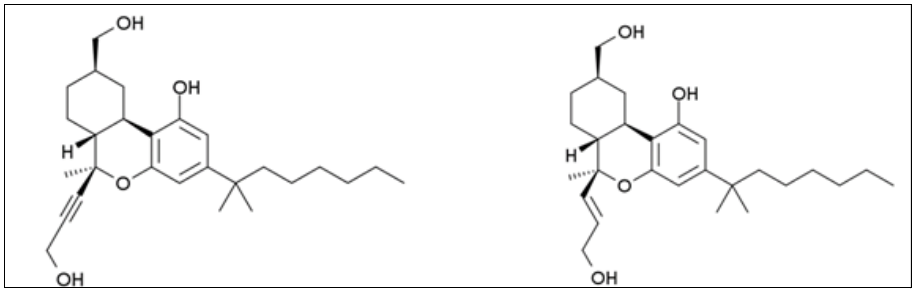

Fig 15: AM-938 (left) and AM-4030 (right)

3.4 Aminoalkindoles

Aminoalkindoles begin to depart from Classical, Non-Classical, and Hybrid synthetics in the way of structural appearance. Most Aminoalkindole NCs do not share structural similarities to classical cannabinoids like THC. Aminoalkindoles are among the compounds most often found in synthetic cannabis blends. This is likely due to the easily accessible papers written by John William Huffman at Clemson University describing the relatively simple methods of production of these synthetic substances [38]. JWH-018 is one of the prime examples of an NC finding its way to the illicit market, as it was one of the first compounds to be used in herbal spice blends and sold under purportedly "All Natural" labels [39].

Following emergency legal action by numerous drug enforcement agencies around the globe, clandestine chemists began to take two different routes of continuing business: 1) Continue research into additional JWH compounds along with other university/corporate compounds of interest 2) Modify existing compounds with confirmed psychoactive properties, a notable example being the JWH-018/073 debacle mentioned previously.

3.5 Eicosanoids

A different approach to NCs come in the form of Eicosanoids. Eicosanoids are a class of oxidized polyunsaturated fatty acids many of which can be synthesized by the body. Some eicosanoids are cannabinoids, aptly named endogenous ones, as they are produced *in situ*. Clandestine chemists have experimented with modifying natural endocannabinoids in order to both skirt regulations and potentially enhance the effects.

These varieties of novel cannabinoids have not found widespread use in the illicit markets, most likely due to manufacturing difficulty. Two notable compounds are of interest in this category AM-356 and AM-404.

AM-356, also known as methandamide, is simply a methylated version of the endogenous cannabinoid anadamide and possess direct binding activity to cannabinoid receptors [40]. AM-404 would be classified as a cannabimimetic, as it prevents the re-uptake of anandamide from neural synapses, the exact mechanism for this action is still being investigated and disputed [41]. Interestingly enough, AM-404 can be synthesized by the body after administration of the popular analgesic acetaminophen. This process occurs when acetaminophen is first de-acetylated into p-aminophenol then enzymatically combined with arachidonic acid to form AM-404 [42]. It is believed that the resulting action from AM-404 as a reuptake inhibitor may be a major factor in the analgesic effect of acetaminophen.

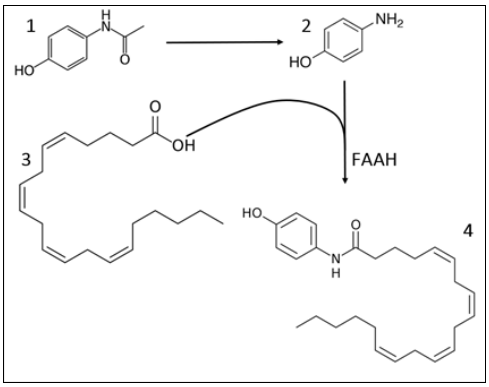

Fig 16: AM-404 synthesis 1) Acetaminophen 2) p-aminophenol 3) Arachidonic acid 4) AM-404

4. Conclusion

To date, there are likely over a thousand NCs in circulation as recreational substances. A major short-term implication of recreational use are severe psychosis, manifesting in aggression, auditory and visual hallucinations, panic attacks, and suicidal tendencies [43, 44]. Other major short-term side effects include tachycardia, myocardial infarction, acute kidney injury, hyperthermia, and rhabdomyolysis [45].

Even more worrisome are the implications of long-term use, as NCs have only been in widespread use for less than 20 years. Some observed long-term implications include possible increased risk for developing psychotic disorders, depression, persistent anxiety, possible increased risk for cardiovascular disease, structural and functional CNS alterations, severe weight loss, and kidney diseases [46, 47, 48, 49, 50].

With constant modification of NCs and new compounds being developed every year, detection of compounds has also struggled to keep up with the stream. In traditional analysis, the lab knows what compounds they should be looking for. With designer drug detection, the lab has to anticipate and adapt to what manufacturers are developing. Rather than looking for whole molecules, labs are searching for traces of common structures found in NCs [51].

It truly is a shame that illicit use of both natural and novel cannabinoids has tainted the therapeutic potential these compounds pose. Currently the world is still recovering from the loss of progress with natural cannabis medicinal value, with legal reforms being undertaken by a large number of countries. Research is beginning now that should have been conducted decades ago. With novel cannabinoids the ramifications could be permanent as they have solidified their place in an almost perpetually vilified state.

5. Acknowledgments

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