White Paper

Eybna's Phytochemical-Receptor Interactions Studies

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Background

Botanical medicine and an “all-natural” products consumption for life quality improvement and longevity are developing into a common approach among a broad part of the population worldwide.

Consumers of different ages and backgrounds are interested in reducing the use of synthetic drugs and chemicals, and seek wellness solutions that are safe, yet predictable and therapeutically beneficial.

Cannabis has been used medicinally for thousands of years for several purposes such as pain relief, mood management, reduce anxiety and sleep aid. However, today there are many barriers in matching the right cannabis product for a specific function.

As cannabis holds a wide range of medicinal potential, the interest to understand its interactions with the human body has grown. The demand to create effective, targeted products and move cannabis consumption from unpredictable into targeted and effective usage has become of a great interest. By diving deeper into the biochemistry of the human body, and using advanced pharmaceutical drug discovery methods, Eybna is unlocking a targeted approach to formulate wellness functional products, with increased efficacy and accuracy for human needs than existing cannabis products.

Chemistry of the Cannabis Plant

The cannabis plant is an immense source of phytochemicals which are known to have therapeutic properties. These properties are generated by interactions between cannabis phytochemicals and receptors in our body.

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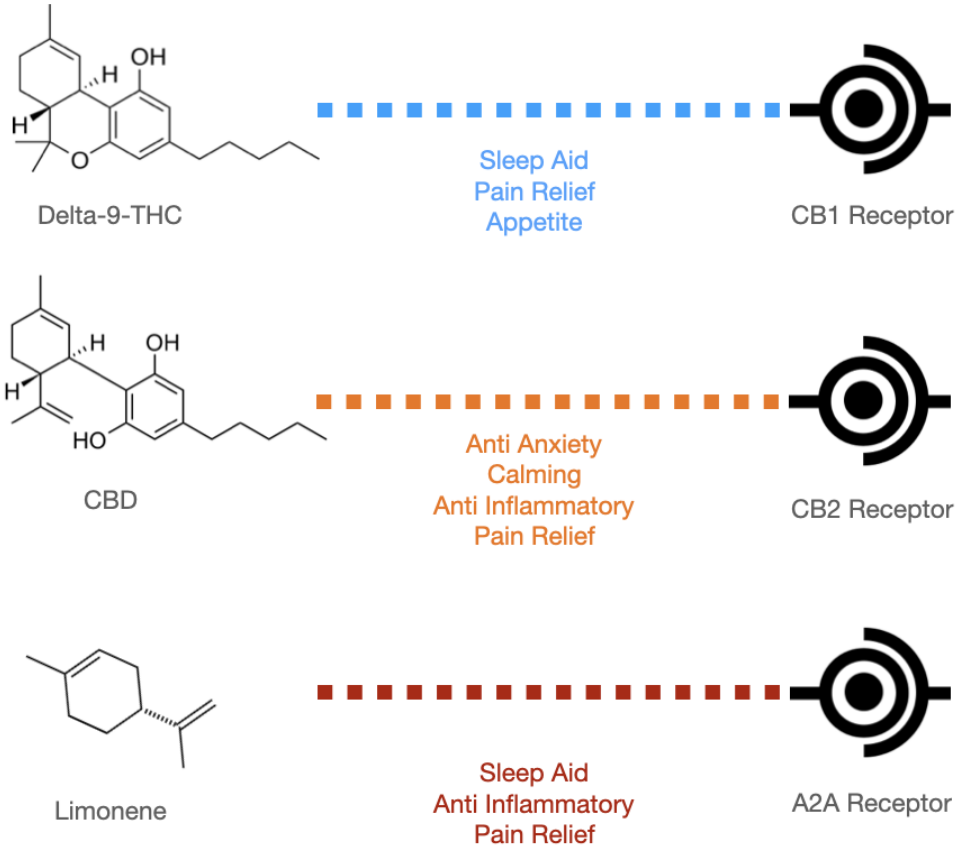


Figure 1: Example of known interactions between receptors and cannabis phytochemicals.

Receptors are chemical structures that respond especially to a particular stimulus. Cannabis phytochemicals have been shown to interact with several biological systems that regulate important physiological processes such as appetite, pain, inflammation, stress response and mood management. These systems are networks of many entities including thousands of receptors.

The Endocannabinoid System

The Endocannabinoid System (ECS) is a biological system composed of several receptors; the most known are the CB1 and CB2 receptors that have been shown to have interactions with cannabis components. Though the ECS is still under research development, it is suggested to play a role in physiological processes. Such as cognitive processes, various activities of the immune system, pain-sensation and memory.

The ECS is widely distributed both in the brain and in the peripheral system, as well as most glands and organs in the body. Within the last decade, Endocannabinoid research has been one of the fastest growing fields in Psychopharmacology and available evidence suggests that there is still a lack of understanding of the varied functions of the Endocannabinoid system. Now we know that not only cannabinoids from the cannabis plant but terpenes and other phytochemicals can also activate this essential system.

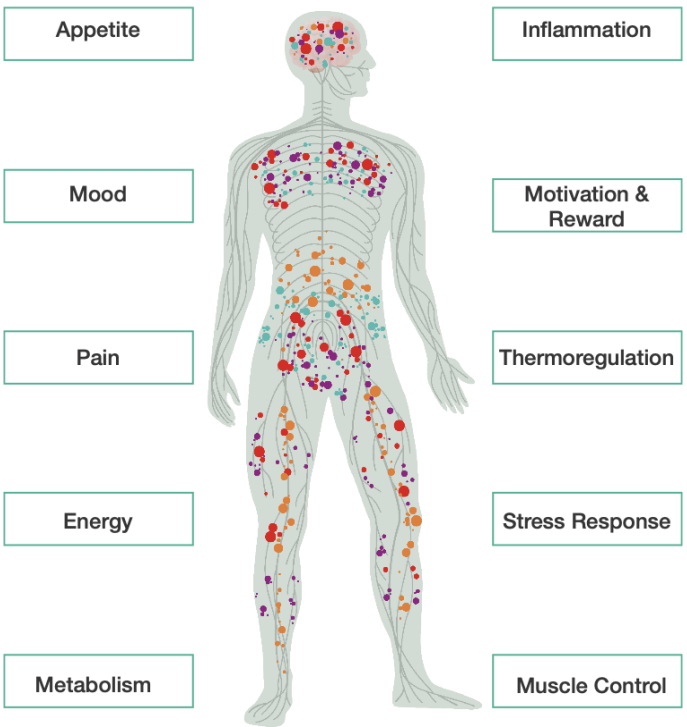


Figure 2: The Body's Endocannabinoid System (ECS) and the major physiological processes it plays a role in.

The Endocannabinoid Receptors

In addition to CB1 and CB2, other receptors are involved in the ECS.
The most notable are transient receptor potential vanilloid-1 (TRPV1), various g-protein receptors (GPR55, GPR13, GPR6, GPR12, GPR18), peroxisome proliferator-activated receptor-γ (PPARγ), serotonin receptors (5HT1A), and adenosine receptors (A2A).[1][2]
The importance of these receptors in the physiological role of the ECS is an area of active investigation.

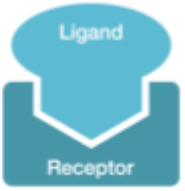
Transient Receptor Potential (TRP) channels are an important pharmacological target for pain management.[3] TRPV1 in particular has become an important target of interest in pain management strategies. Both activators and blockers of TRPV1 can offer therapeutic benefits because receptor stimulation can lead to desensitization, an attractive possibility for chronic pain relief.

Serotonin receptors are activated by the neurotransmitter serotonin. These receptors are notable for known physiological and pathological roles relevant to body temperature regulation, sleep, anxiety and appetite. As well as modulation of higher brain functions including cognition and emotional behavior.

Adenosine receptors found widely, and distributed in almost all human body tissues and organs. Adenosine receptors are commonly known to be inhibited by caffeine which is the mechanism behind the stimulating effects of coffee. Adenosine 2A (A2A) receptor has broad anti-inflammatory effects throughout the body, and a sedative or stimulating effect when activated or inhibited, respectively.

Receptors 101:

- Receptors are proteins embedded in cell membranes to which **ligands**, such as neurotransmitters or drugs, bind and initiate a response.
- A common analogy for receptor-ligand interaction is "a lock and key".
- A ligand's ability to affect a given receptor is related to the molecule's affinity to a receptor.
- Physiologic functions are usually regulated by multiple receptor-mediated mechanisms.



Phytochemicals Interactions with Endocannabinoid System

The potential medicinal benefits of phytochemicals and the mechanisms by which they interact with the ECS are of great interest for the medicinal and therapeutic application of cannabis.

The discovery of the cannabis phytochemicals has led to the further discovery of the potential medicinal values for several indications, and in recent years, cannabis terpenes have begun to be treated as active ingredients and not just cannabinoids. For example, the sesquiterpene beta-caryophyllene has been shown to have analgesic effects in mouse models of neuropathic pain and peripheral neuropathy, suggesting the effects are mediated via the CB2 receptor. [4][9]

Overall, numerous studies support the anti-inflammatory and analgesic effects of beta-caryophyllene, and its pharmacological activity as an agonist at CB2.[3][5] In addition, the monoterpene beta-myrcene has been reported to have activity at TRPV1 receptors which may lead to pain relief properties.[6] Furthermore, CBD has been shown to be a direct agonist at serotonin 5-HT1A receptors, TRPV1 receptors, and an indirect agonist at adenosine receptors which explains its wide therapeutic benefits.[2]

Out of the hundreds of phytochemicals found in cannabis, only a couple are deeply studied. Very few studies have made any attempt to identify the exact molecular targets and mechanisms for all compounds found in cannabis.

Biologically-Based, Data-Driven Approach

Eybna harvests the combined powers of advanced research and pioneering technology to utilize natural compounds. Advancing cannabis consumption from unpredictable into targeted and effective usage.

Eybna studies the interactions between cannabis phytochemicals and the human body using advanced methodologies that are commonly used in the drug discovery world.

In order to test a wide range of compounds' biological activity, Eybna uses a High-Throughput Screening (HTS) method. This method identifies compounds that can activate or inhibit specific receptors or targets in the human body. This method permits large compound collections to be screened against diverse, biologically relevant targets in a high throughput fashion.

By doing so, Eybna assesses the biological activity of hundreds of phytochemicals *in vitro* both alone and in combination against receptors of interest to detect biologically-active compounds. The chosen receptor targets for Eybna's HTS are related to most frequently reported indications for which medical consumers use cannabis. Some of the targeted receptors that were used in the study and the associated indication are presented in Figure 3.

In addition to *in vitro* studies, Eybna utilizes advanced computational biology methodologies that allow the prediction of the interactions between phytochemicals and receptors. This method involves machine learning algorithms and is commonly referred to "in silico".

The above - mentioned techniques generate large data sets that hold the quantitative measurements of the biological activity of phytochemicals on receptors targets - Eybna's building blocks for creating targeted formulations.

Figure 3: The main receptors of Eybna's research which have been shown to have some interaction with cannabis phytochemicals.

The Largest Database of Phytochemicals

Eybna generates and collects biological data through advanced scientific methods from drug-discovery techniques to AI computer simulations. These large data sets reflect the biological activity of phytochemicals on specific body receptors.

Eybna's database encompasses information on more than 500 phytochemicals including their quantitative biological activity versus specific receptors derived from both HTS and computer-generated biological predictions. In addition, the database includes biological activity data from existing studies found in published scientific journals as well as safety, chemical and physical properties of the compounds (Figure 4).

These large data sets are fed to Eybna's database and used for the development of Eybna's functional formulations, including Eybna's Receptor Specific formulations.

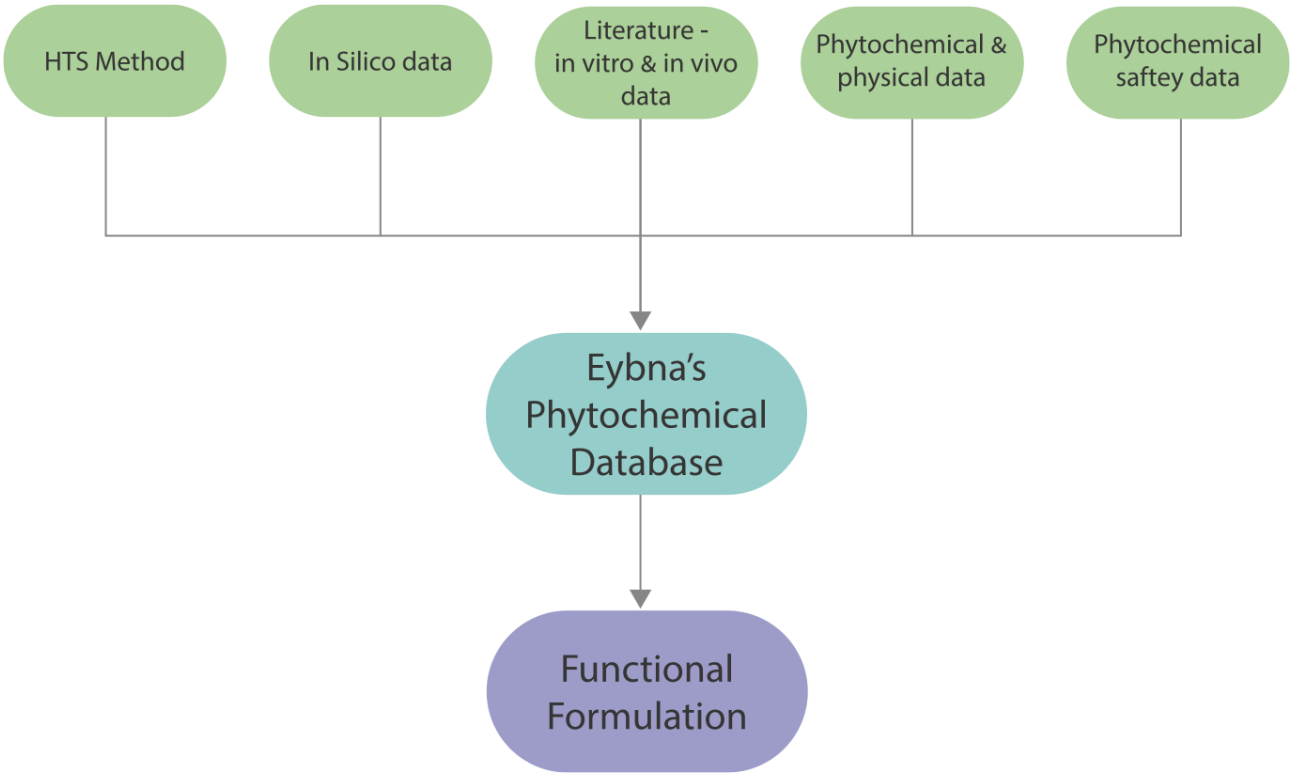


Figure 4: The components of Eybna's Phytochemical Database

From Data Science To Functional Formulations

Eybna studies every single compound and its relationship with body receptors. Eybna's Receptor-Specific™ formulations introduce data-driven botanical formulations engineered to modulate specific receptors in our body. These receptors are associated with important physiological processes such as focus, sleep, pain, inflammation, anxiety and mood management.

Eybna's novel botanical Receptor-Specific™ formulations are engineered to achieve specific functionalities and feelings:

CB1 Receptor-Specific™ formulation
This formulation is designed to activate the CB1 central receptor in the Endocannabinoid system. The CB1 receptor is known to be activated by Δ^9-THC and associated with pain relief and sleep aid.

CB2 Receptor-Specific™ formulation
This formulation is designed to activate the CB2 receptor in the Endocannabinoid system. The CB2 receptor is known to be activated by CBD and associated with anti-anxiety and anti-inflammatory properties.

5-HT3 Receptor-Specific™ formulation
This formulation is designed to activate the 5-HT3 receptor in the Serotonergic system. The 5-HT3 receptor is known to be activated by Psilocybin and associated with cognitive functions such as focus, learning and memory.

TRPV1 Receptor-Specific™ formulation
This formulation is designed to activate the TRPV1 receptor in the Endocannabinoid system. The TRPV1 receptor is known to be activated by CBD and Capsaicin. It is associated with the treatment of inflammation and pain perception.

GPR55 Receptor-Specific™ formulation
This formulation is designed to activate the GPR55 receptor in the Endocannabinoid system. The GPR55 receptor is associated with inflammatory and neuropathic pain as well as anxiolytic activity.

A2A Receptor-Specific™ formulation
This formulation is designed to activate the Adenosine A2A receptor that is considered part of the Endocannabinoid system. The activation of the A2A receptor affects various behaviors including locomotor activity, sleep-wake cycle, anxiety, depression and learning and memory.

GABA232 Receptor-Specific™ formulation
This formulation is designed to activate the GABA232 receptor in the GABAergic system. The GABA232 receptor activation affects anxiety and sleep regulation.

GABA132+ Receptor-Specific™ formulation
This formulation is designed to activate the GABA132 receptor in the GABAergic system. The GABA132 receptor activation affects sleep cycle regulation as well as muscle relaxation.

GABA132- Receptor-Specific™ formulation
This formulation is designed to inhibit the GABA132 receptor in the GABAergic system. The GABA132 receptor inhibition associates with focus and stimulating effects.

GABA332 Receptor-Specific™ formulation
This formulation is designed to activate the GABA332 receptor in the GABAergic system. The GABA332 receptor activation affects sleep cycle regulation, muscle relaxation, and pain .

Eybna's Receptor-Specific™ formulations empower the next generation of wellness products, address consumers' most in-demand needs and provide worldwide brands in the CPG, wellness and cannabis markets the opportunity to unlock new targeted and specific experiences, all backed by science.

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