HEEROMA BIOMEDICAL

CANNABIS-BASED MEDICINE CONSULTANCY

WHITE PAPER

2022

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White paper

Index:

Cannabis medically revisited

Cannabis is getting a lot of media attention lately. Its image is rapidly shifting from gateway drug to universal cure. What people may have missed though, is why cannabis is suddenly receiving all this positive attention.

The endocannabinoid system guards life's most critical functions

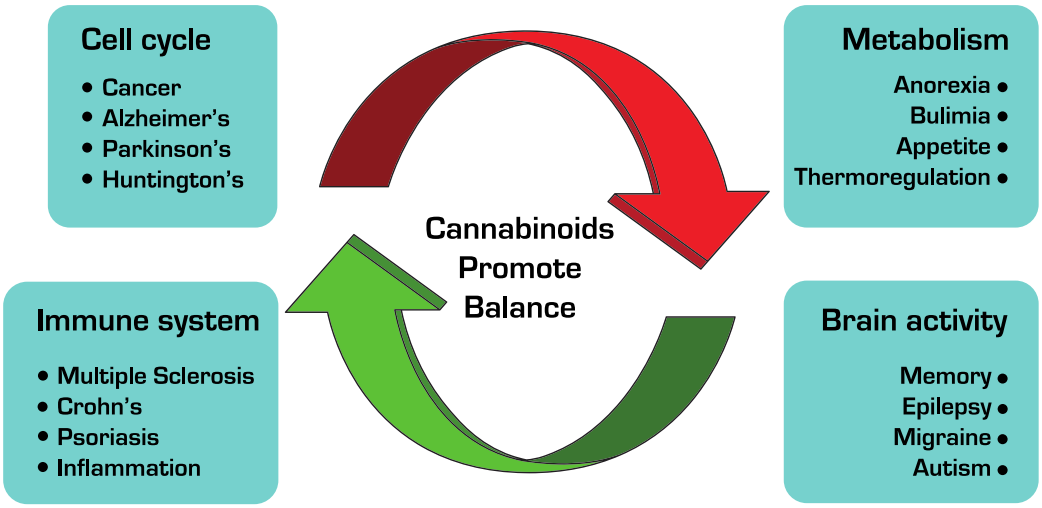
The reason for this revolution is a fairly recent discovery in biology: the endocannabinoid system. The endocannabinoid system originated several hundred million years ago, roughly when single-celled life evolved into multicellular organisms. This required new regulatory mechanisms to govern life's most critical functions such as cell division, metabolism, the immune system and brain activity (Figure 1).

Failure to control cell division may lead to cancer on the one hand and to degenerative diseases like Alzheimer's, Parkinson's or Huntington's on the other.

Similarly, energy levels need to be tightly controlled. Failure to do so can lead to anorexia on the one hand and bulimia or diabetes on the other. A strong connection between cannabis and metabolism has always been suspected, but now science is uncovering the underlying mechanism.

Being able to discriminate self from non-self is another crucial condition for life. Failure results in autoimmune disease like irritable bowel disease, multiple sclerosis, psoriasis or debilitating infection.

Figure 1: The endocannabinoid system guards life's most critical functions



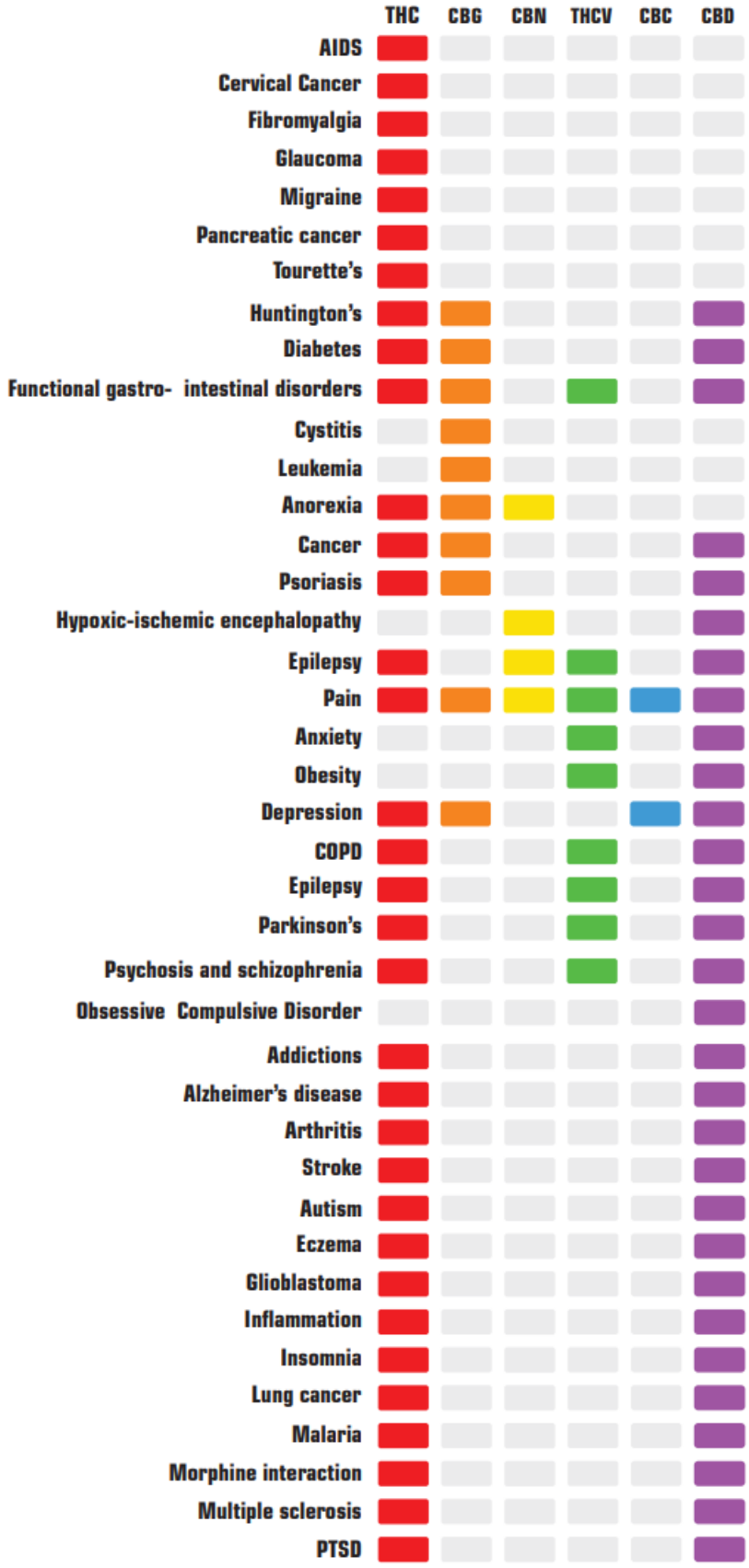
Many diseases are due to a dysfunctional or overpowered endocannabinoid system
Plant cannabinoids can boost the endocannabinoid system

Finally, intelligent life requires tight control of behavior or brain activity. Failure to maintain this balance can manifest itself as anxiety, attention deficit hyperactivity disorder, obsessive-compulsive disorder, schizophrenia or depression. Cannabis use has often been associated with these diseases. Only where cannabis was usually blamed for causing mental disorders, it is now increasingly recognized that many people are genetically predisposed to and might actually self-medicate to stave off these very disorders.
Combined, a picture emerges where many seemingly distinct diseases share a common defect: a dysfunctional or overstressed endocannabinoid system. Since endocannabinoids are functionally very similar to plant cannabinoids, plant cannabinoids can be exploited to boost the endocannabinoid system and promote mental and physical balance. This is the key to the therapeutic potential of plant cannabinoids.

Cannabinoids can alleviate symptoms or even cure disease

The therapeutic use of cannabinoids goes back thousands of years to places like India and China where cannabis was recommended for malaria, dysentery and constipation, to block rheumatic or menstrual pain, to induce sleep and to stimulate appetite.
Unfortunately, much evidence for the therapeutic value of cannabinoids is anecdotal and not backed by scientific method. Still, a wealth of scientific data exists that supports the therapeutic use of cannabinoids.
To date, there is scientific evidence for the therapeutic value of cannabinoids in many disorders (Figure 2). This includes some of the most debilitating and financially burdening diseases in the developed world: Alzheimer's, cancer, depression, diabetes, epilepsy, obesity, pain and others. For a detailed description of this evidence please see: (https://ghmedical.com/diseases). This list is likely to grow, as any disorder marked by unbalanced cell division, metabolism, immune system or brain activity is potentially eligible for cannabinoid therapy.

Figure 2: Diseases linked to the endocannabinoid system and therapeutic potential of cannabinoids



What are the major cannabinoids?

THC

After the prohibition of cannabis in the early 20th century, (black market) breeding primarily focused on the recreational or psychotropic effects of cannabis, in other words: THC. THC promotes euphoria and sleep and reduces stress, memory and cognitive performance. These effects are popular with recreational cannabis users but are also very useful for the treatment of insomnia, depression, anxiety, and post-traumatic stress disorder for instance. The ability to forget seems increasingly useful in our modern, stressful society. Apart from sleep and amnesia, THC also stimulates appetite and reduces nausea, pain and inflammation, which can be very useful in the treatment of cancer or the side effects of cancer medication. Preclinical research even suggests that THC can actually stop cancer cells from dividing and for instance brain cells from an Alzheimer's patient from degenerating. Interestingly, although THC usually impairs memory, in aged mice THC seems to actually improve cognitive function, suggesting the effect of cannabinoids is actually situation-dependent. In short, THC is the main psychotropic cannabinoid but it has phenomenal therapeutic potential too.

CBD

Apart from illegal cannabis for recreational purposes, cannabis was also cultivated for industrial purposes: fiber hemp was specifically bred for its fibers, which can be used for clothes, paper, concrete and many other applications. However, fiber hemp also produced CBD as a side product. CBD is not psychotropic and can even be used to counter the psychotropic effects of THC thus potentially increasing the therapeutic potential of THC. Although CBD is not psychotropic/euphoric it is still psychoactive: CBD has therapeutic potential in the treatment of insomnia, anxiety, depression and obsessive compulsive disorder for instance. Also, CBD is anti-psychotic making it potentially useful in the treatment of psychosis and schizophrenia. Where THC is an appetite stimulant, CBD seems to reduce appetite, suggesting a use in the treatment of obesity or diabetes. Like THC, CBD shows promise as an anti-cancer agent. CBD seems to have even stronger anti-inflammatory properties than THC making it useful in a whole range of immune disorders such as eczema or multiple sclerosis. Finally, CBD appears to have excellent potential as anti-epileptic medicine. In fact it is this property of CBD that has fuelled much research and driven the re-evaluation of cannabis as a medicine.

THC is the main cannabinoid in recreational cannabis and CBD is dominant in fiber hemp. However, both types of cannabis also contain trace amounts of other cannabinoids. Since these 'minor' cannabinoids are relatively rare not much is known about their physiological and therapeutic properties (see below). Landraces, which are original varieties that have not been changed by breeding programs, may provide a solution. These landraces are likely to still contain cannabinoids other than THC and CBD in appreciable amounts. In the future, selective breeding programs should generate cannabis varieties that are dominant in these 'minor' cannabinoids so that their therapeutic potential can be fully explored.

CBG
CBG is a precursor from which both THC and CBD are derived. However, CBG also possesses therapeutic properties of its own. Like CBD, CBG is not psychotropic. CBG appears to be a stronger appetite stimulant than THC making it useful in anorexia for instance. In addition CBD has some anti-inflammatory and anti-cancer properties, which need to be further explored.

CBC
CBC is not psychotropic and may have a future role in the treatment of depression and pain but the true therapeutic potential of CBC still needs to be researched.

CBN
CBN is a degradation product of THC, which may have some psychotropic properties when used in combination with THC. CBN may be useful in the treatment of pain and ischemic events (such as stroke) but more research is required.

THCV
THCV has psychotropic properties that are similar to, but distinct from, THC. Very preliminary results indicate that THCV may be therapeutic in the treatment of anxiety, obesity, diabetes, functional gastro-intestinal disorders, epilepsy and pain. Again, more research is required to explore the full therapeutic potential of THCV and other cannabinoids.

Figure 2 shows that many cannabinoids have overlapping spectra of diseases they are linked to. For instance many cannabinoids have some effect in pain management or in the treatment of epilepsy, depression, diabetes and functional gastro-intestinal disorders. This reflects that cannabinoids have similar but distinct effects and also that depending on the person or disease it may be beneficial to try different combinations of cannabinoids until the optimal formulation is found.

Acidic cannabinoids

In daily practice we say that THC, CBD etc. are produced by cannabis but strictly speaking this is not true. Cannabis produces acidic cannabinoids, which are then degraded to their chemically neutral variants, the cannabinoids that we know. In other words cannabis produces THCA (for THC-acid), which is subsequently converted by heat and/or light to THC. Similarly, CBD, CBG, CBC and THCV are degradation products of CBDA, CBGA, CBCA and THCVA respectively. Contrary to THC, THCV and to some extent CBN acidic cannabinoids are not psychotropic. Also, due to their chemically acidic nature acidic cannabinoids are more hydrophilic/water soluble which may change their biological availability and distribution through the body. This is relevant as it looks like acidic cannabinoids may have therapeutic properties of their own. To which extent acidic cannabinoids are therapeutic or change the

therapeutic properties of chemically neutral cannabinoids remains to be seen as acidic cannabinoids are even less investigated than the regular ones.

Orphan cannabinoids

We have so far discussed the six major cannabinoids and their acidic counterparts but detailed chemical analysis has actually revealed more than one hundred cannabinoids in cannabis. By analogy to the cannabinoids we already know, these cannabinoids are likely to possess therapeutic qualities of their own. However, like the so-called minor cannabinoids discussed above, these cannabinoids are simply not around in sufficient quantities to research their therapeutic properties. Again, it is therefore crucial that we revert our attention to landraces, untouched by human hands or breeding programs and start focusing on these minor and orphan cannabinoids to unleash the full therapeutic potential of cannabis.

Terpenes

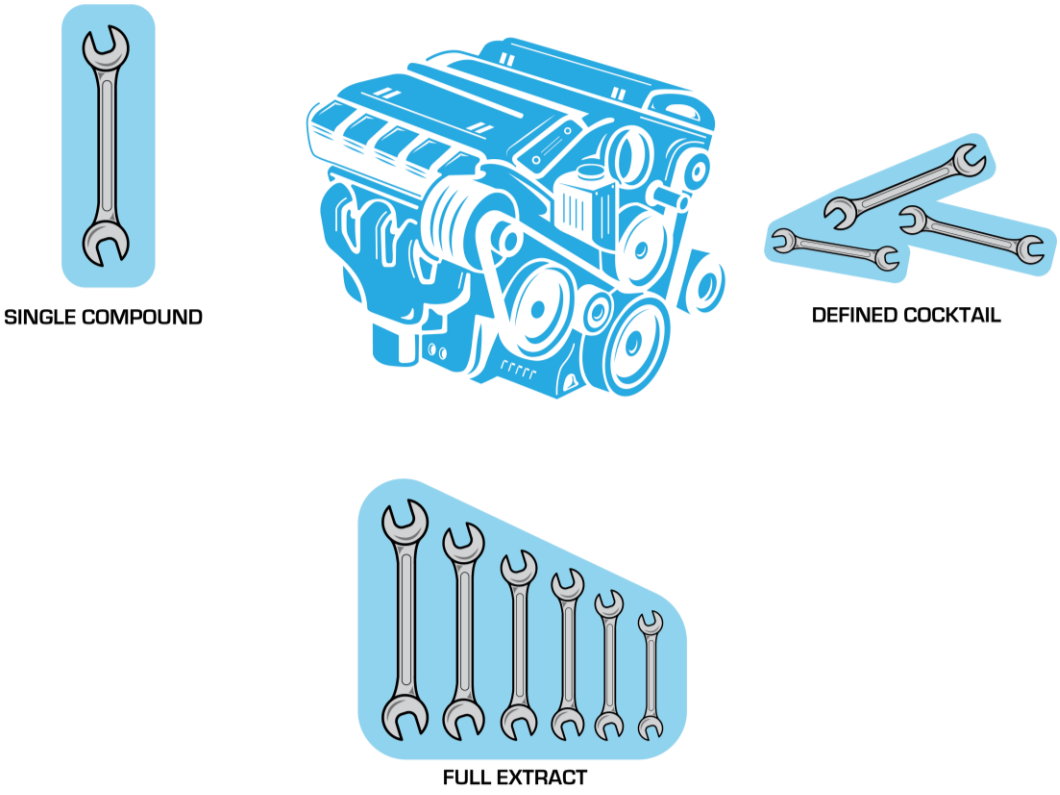
Cannabinoids are not the only class of active compounds in cannabis; cannabis also produces terpenes. Terpenes are the aromatic compounds that constitute 'essential oils'. Apart from being responsible for the characteristic smell and taste of many herbs and fruits, terpenes also exert a strong effect on our body/physiology. This is best exemplified by strain differences observed in recreational cannabis; recreational strains are usually selected based on their smell (read terpene profile) and most users will attest that different strains of cannabis can have dramatically different effects on the perception of feeling high, stoned, relaxed, anxious, hungry or tired. Now when we look at the chemical profile of recreational cannabis, almost all strains will have a highly similar cannabinoid profile (high in THC and low in other cannabinoids). These strains however do have different terpene profiles and science is uncovering their effect more and more. Terpenes have anti-bacterial, anti-inflammatory, anti-parasitic, anti-anxiety, anti-depressant and anti-cancer effects, to name but a few of their functions. Also, terpenes seem to address the same cellular targets (receptors, discussed below) as cannabinoids. Therefore, where cannabinoids are regarded as the main driving force behind the effects of cannabis, terpenes can be seen as the steering wheel, fine-tuning these effects and giving them direction.

Entourage effect

The principle described above where the effect of cannabinoids is altered by terpenes is an important aspect of cannabis-based medicine: the entourage effect. Cannabinoids have very similar, yet distinct functions in our body, which is reflected by the overlap and differences in the diseases that various cannabinoids can address (figure 2). Another interesting finding is that single isolated cannabinoids may be effective in treating a particular disease but they are often outperformed by full botanical extracts, which contain traces of many cannabinoids and terpenes in addition to the single cannabinoid of interest. Single cannabinoids typically have a sharp optimum concentration for the desired effect and both lower and higher doses give suboptimal

effects. Full botanical extracts on the other hand appear to be more tolerant towards (mis-) dosage and typically work better at higher concentrations. This effect may seem illogical but is possibly explained by the following analogy: let's compare a disease with a broken engine and cannabinoids and terpenes with wrenches of different shapes and sizes (figure 3). While it is possible to fix a broken engine with only one or a few wrenches (isolated compounds), it requires a lot of insight into which parts of the engine are actually broken. However, if you have a full set of wrenches (full botanical extract), you are much more likely to be able to fix the engine, even without knowing beforehand which parts are broken. Therefore, until we know exactly how a disease works mechanistically, it is probably wiser to use full botanical extracts rather than guessing which cannabinoids or terpenes are relevant to any particular disease. How the entourage effect works exactly is still a matter of debate and requires a lot more research but the entourage effect is certainly relevant and intriguing.

Figure 3 : Entourage



Cannabinoid receptors

Just as there are more cannabinoids than just THC, there is more than one cannabinoid receptor (which translates the 'function' of a cannabinoid to a physical effect). To date, we have found 42 receptors that are activated, blocked or otherwise modulated by cannabinoids. Some of these receptors are so called 'true' cannabinoid receptors (CB1 and CB2). Other receptors like GPR55 or TRPV1 for instance, were originally described as members of other

regulatory systems that happen to interact with cannabinoids as well. The exact mechanism of action for these receptors is still under investigation and goes beyond the scope of this overview. However, a quick glance over their respective functions reveals that cannabinoid receptors have a regulatory role in: cell division, metabolism, the immune system, neuronal function in both the central and peripheral nervous system, cardiovascular function, gastro-intestinal function, bone metabolism, stress regulation and pain regulation. Thus, with 18 endocannabinoids, 32 plant cannabinoids (with known function) and 42 cannabinoid receptors we can see a cannabinoid network emerging with huge regulatory power and thus vast therapeutic potential.

Routes of application

Apart from finding the right cannabinoid cocktail, the route of application is equally relevant to devise optimal treatment for any particular disorder (Figure 4).

Inhalation

Smoking is of course not healthy. In addition, smoking incinerates about 30% of the available cannabinoids. Therefore vaporizing cannabis/cannabinoids may be a healthier and more economic solution. Either way, the majority of medical cannabis patients prefer to smoke/vaporize their cannabis. This is probably because inhaling cannabis is relatively fast in onset and easy to dose. So what happens when someone inhales cannabis? Most cannabis on the market is very high in THC and contains relatively low amounts of other cannabinoids. The level of THC in blood rises sharply and peaks roughly ten minutes after starting to smoke. THC is then metabolized, mostly by liver enzymes, causing THC levels to drop, fast at first and then gradually more slowly until the THC level is back to normal after about six hours.
Of the 42 cannabinoid receptors identified so far, 18 can be activated by THC. Some of these receptors will be activated by very low levels of THC, meaning they will be active for a relatively long period of time within the six-hour window mentioned above. The CB1 receptor is an example of this, which explains why people can feel high or stoned for hours after smoking a joint. Receptors that are activated by higher cannabinoid concentrations will consequently be active for a shorter amount of time after inhaling. There are also receptors that require such high amounts of cannabinoids that they are never activated after inhaling (in the case of THC this goes for 8 out of 18 receptors). This means these receptors cannot be activated by inhalation and thus that another route of application is required (for instance topical application).
For CBD the situation is different. Most commercially available cannabis is high in THC and low in CBD. Therefore, even though 19 receptors can potentially be activated by CBD, none of these are activated by the amount present in commercial cannabis. Luckily over the years more medicinal strains have become available that contain CBD levels sufficient to activate some receptors. Alternatively high-CBD extracts can be used, topical or otherwise to activate receptors for CBD.

For other cannabinoids like CBC, CBG, CBN and THCV for instance, the situation is even more complex. Since there are hardly any strains available that contain appreciable amounts of these cannabinoids it is very difficult to obtain the effects of these cannabinoids via inhalation. Again, extracts or isolated cannabinoids may be of some medicinal value, but for large-scale use new stains are required that do produce these cannabinoids.

Oral
When eating cannabinoids, the effect takes a lot longer to start, peak and taper off. However, ingested cannabinoids are bathed in stomach acid first and then partially metabolized the liver, severely limiting cannabinoid bioavailability[1].

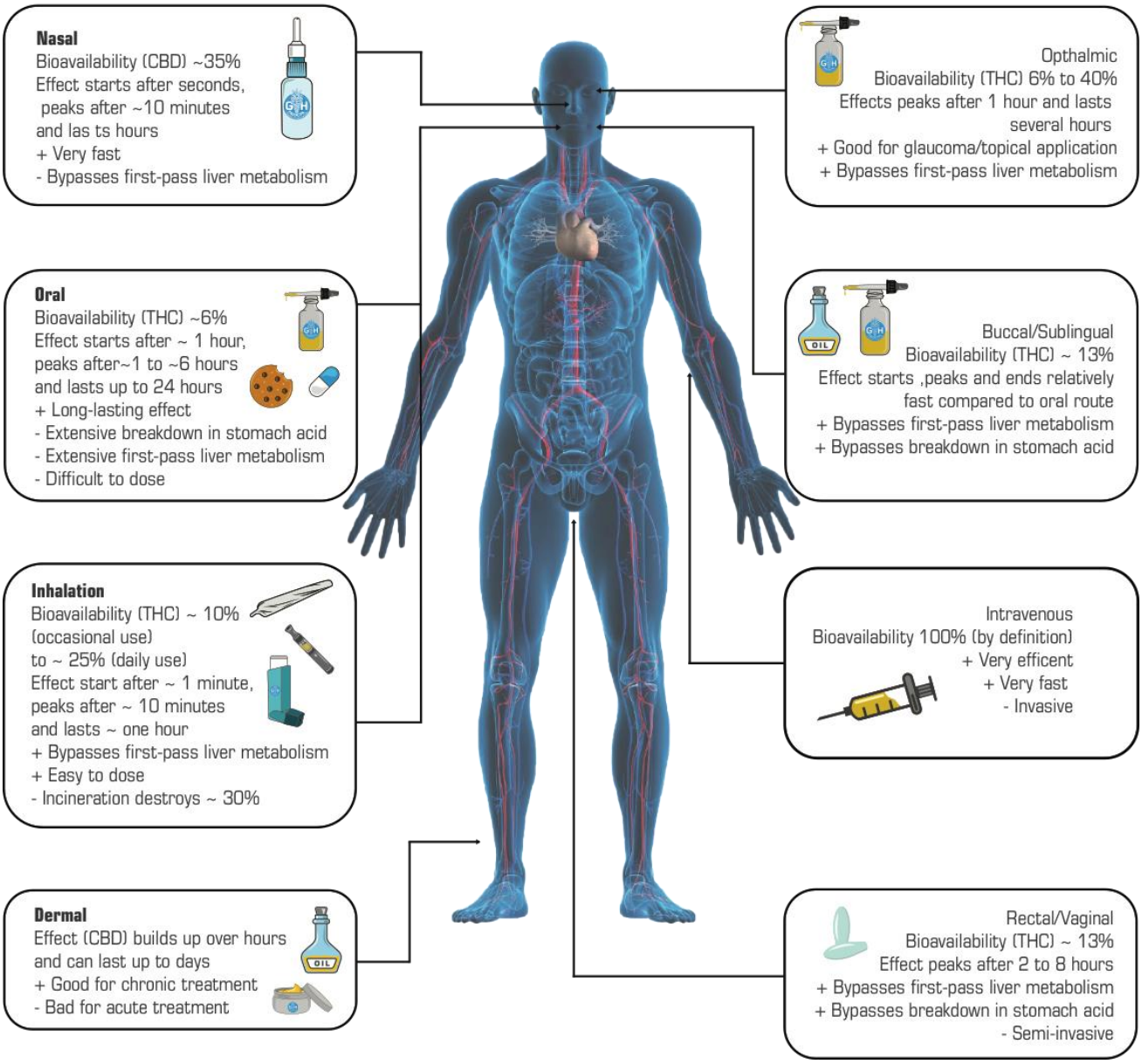
Sublingual
Applying cannabinoids to the mucous membranes in the mouth (tongue, cheek, pallet or gums) rather than ingesting them doubles bioavailability and dramatically reduces the 'time-to-effect'. Similar but distinct effects are reached by rectal or vaginal application.

Topical
Application to the skin takes hours to take effect but the effect can last up to days. Topical application is slow in onset, long in duration and, importantly, does not produce psychoactive side effects.

Nasal
Alternatively cannabinoids delivered by nasal spray can take effect in seconds.
Thus, depending on the desired effect different routes of application might be preferred.

[1] Bioavailability is a measure for the percentage of a biologically active substance that is available for a reaction. By definition injected compounds have a 100% bioavailability and every other route of application is compared to that.

Figure 4 : Route of application



Safety, adverse effects and dosage

Documented use of cannabis goes back thousands of years and according to the World Health Organization there are currently over 180 million cannabis users worldwide. Still there are no documented deaths relating directly to cannabis use. This means that the use of cannabis or cannabinoids is very safe from a toxicological point of view, basically unparalleled by any other medication[2]. Consequently this means that is safe for consumers to experiment which cannabis strain or cannabinoid (cocktail) works best for their particular ailment. Although cannabinoids are safe to use, some consumers do experience adverse effects. For THC these are usually memory impairment, anxiety, increased heart rate, red/dry eyes, dry mouth or vertigo. In some cases THC can cause paranoia or precipitate a psychosis-like state. Some, but certainly not all, chronic users may experience motivational problems. CBD comes with far fewer adverse effects but especially at higher doses some users may experience diarrhea, feeling tired or alternatively insomnia. For other cannabinoids it is not yet known whether they elicit adverse effects.
Although there is no universal dosing protocol it is generally advised to 'start low and go slow' meaning start with one or drops/puffs/milligrams, observe the effects and if required increase dosage in small steps. When adverse effects become noticeable go back to the previous dosage.

Scientific justification and extra reading material

This is just a very basic introduction to medicinal cannabis and the rationale behind its therapeutic potential. The information in this white paper is extracted from over 10.000 scientific publications about cannabis-based medicine in the HEEROMA BIOMEDICAL database. For more information, please visit heeromabiomedical.com or book a consultation.

About the author

Joost Heeroma is a biomedical researcher with a PhD in Functional Genomics. Joost studies how our individual genetic passports determine how we behave, which diseases we are likely to get and how these diseases are best treated. Central to his studies is homeostasis; a collection of biological feedback mechanisms that keep the body in balance and free from disease. Joost currently studies the greatest group of all feedback regulators: cannabinoids. Joost is the owner of HEEROMA BIOMEDICAL and a board member of Cannabinoid Association Netherlands/CAN. He provides expert advice on cannabis-based medicine product formulation, -clinical trial design, -education and regulatory issues and is available for private consultation.

[2] It is important to note here that synthetic cannabinoids absolutely do not share the safety record of natural or plant cannabinoids. Synthetic cannabinoids kill people on a daily basis and should be avoided unless specifically prescribed by a healthcare professional.