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**The effects of Cannabigerol on Muscle, Joint & Bone**

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**Athlete's interest in muscle, bone, tendon & joint**

It is well known among athletes that some discomfort and pain is part of athletic activities and is often part of a successful training program. For muscle strength to increase, the muscle must see some increase in stress over what it is used to experiencing, and this stress is usually perceived as the “burn” in muscle during activity. This mild burn is what we call "good pain" and is the basis of the popular phrase - "No pain, no gain." This pain should be short-lived and resolve soon after the activity ends.

Fatigue after a good, strenuous workout is also a sign that the exercise is pushing the limits of the athlete’s physiology, but it too should not be excessive. This fatigue should leave the individual somewhat exhilarated but not overly exhausted. Fatigue that lasts days means the individual’s physiology has been excessively challenged, and this means that the muscles and the energy stores are not being effectively replenished. Chronic fatigue after excessive exercise suggests that the individual may be overtraining. If after appropriate rest the fatigue continues, it may be a sign of other medical problem called "bad pain".

The muscles, tendons, ligaments, cartilage and bones of the body are living structures that react to the stress of exercise only gradually. If they see stress too fast, they cannot respond effectively and may begin to fail. The causes of the failure can be too much stress too fast, or it can be the accumulation of excessive stress over time. When this occurs, each one of these tissues responds a little differently.

**Muscle** soreness typically occurs if you do a new exercise to which you are not accustomed or if you do a familiar exercise too hard. This soreness typically begins within a few hours but peaks one to two days after exercise. This soreness is called delayed onset muscle soreness and may represent actual muscle damage. A little soreness or discomfort means that the muscle has been stressed, but if the muscle is exercised too much, the muscle can become very sore to move and touch and may even swell. In severe cases, the muscle may be damaged to the point that the muscle starts to develop permanent damage. It is generally recommended that if you start an exercise program, you begin very slowly and build up gradually.

**Tendons & ligaments** that connect muscle to bone may get irritated if they see too much stress too rapidly. They respond by getting inflamed, which is characterized by pain and sometimes swelling. Tendinitis pain typically occurs during exercise and can continue afterward when performing activities using that muscle or tendon.

**Bones** need time to respond to new stress. When bones see increased amount of stress, they gradually respond by putting more bone in the areas of the bone that are seeing more stress. This response is called **re**modeling and strengthens the bone. However, if the area of bone sees stress too fast, the bone will actually begin to fail. The first sign of this stress reaction is pain along the bone, which occurs with activity. As the situation worsens, a stress fracture can develop. This may result in a limp and even pain at night. If untreated the bone can actually break, which can be a severe injury.

**Cartilage** is the slippery white tissue on the ends of the bones in the **joint** that allows the bones to glide and move smoothly over one another.Cartilage also needs stress applied very gradually. As a person matures, it is common for the cartilage to see some wear & tear so that it is not perfectly smooth. When the cartilage sees too much stress too rapidly, it can result in pain and fluid accumulating in the joint. Swelling in a joint is a worrisome sign meaning that the cartilage is irritated. If the **inflamed joint** is not rested, the pain and swelling can increase and result in functional problems.

**Sports & physical exercise performance issues**

Exercise, particularly when strenuous, unfamiliar, and involving an eccentric components, can cause ultra-structural damage to skeletal **muscle myofibrils** and the surrounding extracellular matrix. This exercise-induced muscle damage (**EIMD**) impairs muscle function and initiates an inflammatory response. While inflammation is integral to EIMD repair, regeneration and adaptation - excessive inflammation may contribute to prolonged muscle soreness and delayed functional recovery. Persistent pain is common in athletes. Nociceptive pain, which includes inflammatory pain, typically occurs with tissue damage; whereas neuropathic pain typically results from a lesion or chronic disease in the somatosensory nervous system. Neuropathic pain is common among athletes and can also arise if there is repetitive mechanical or inflammatory irritation of peripheral nerves.

While the beneficial effects of high-impact exercise on **bone** health are well established, other factors within the sporting context (traumatic injuries, low energy availability) may cause or contribute to reduced bone health and the development of fractures in athletes.

**Heat loss** **mechanisms** play a pivotal role in the maintenance of homeostasis during exercise. Any treatment or condition that alters core body temperature therefore has the potential to impact exercise performance.

High levels of **pre-competition stress**, or **sports performance** **anxiety** (**SPA**), can be detrimental to athletic performance. This impairment has been attributed to both the direct (anxiogenic) and indirect (decreased nutritional intake, increased energy expenditure, loss of sleep) effects of SPA. While behavior therapies (such as cognitive behavioral therapy [**CBT**]) are the preferred treatment, a combination of pharmaceutical and psychological interventions may be indicated in some cases.

The importance of **adequate sleep** in facilitating optimal athletic performance and recovery is increasingly recognized. Yet, athletes often sleep less (6.5 hours per night) and experience poorer quality sleep than non-athletes. Factors that contribute to poor sleep among athletes include: prolong training sessions, pre-competition anxiety, use of caffeine, and long-haul travel (jet lag, travel fatigue). If an athlete develops **pain** after exercise, he should rest or decrease the activity that is causing the problem, ice the painful area, keep moving gently and consider medicines to treat the **anxiety**, **pain** and **inflammation**.

Both acute and overuse musculoskeletal injuries are common in athletes. **Pharmacologic agents** including non-steroidal anti-inflammatory drugs [**NSAIDs**], **acetaminophen** (Paracetamol), **opioids** and topical over-the-counter agents have been shown to be effective in controlling pain, but data regarding their safety, efficacy in expediting healing and time to recovery continue to be debated. Studies indicate that athletes consume analgesic agents on their own and may be unaware of their potential toxicities. Data also indicate athletes use medications in hopes of alleviating pain and allowing continuation of sports without adequate time for healing.

**Paracetamol,** also known as acetaminophen, is a medication used to treat fever and mild to moderate pain**.** It is used for the relief of headache, muscle aches, minor arthritis pain, toothache as well as pain caused by cold & flu. It is recommended, in particular, for acute mild to moderate pain, since the evidence for the treatment of chronic pain is insufficient. In the short term, common side effects of paracetamol are nausea and abdominal pain, and it seems to have tolerability similar to ibuprofen. Chronic consumption of paracetamol may result in a drop in hemoglobin level indicating possible gastrointestinal bleeding and abnormal liver function tests. There is a consistent association of increased mortality as well as cardiovascular (stroke, myocardial infarction), gastrointestinal [GI] (ulcers, bleeding) and renal adverse effects with taking higher dose of paracetamol. The drug may also increase the risk of developing hypertension. Elevated frequency of asthma and developmental and reproductive disorders is observed in the offspring of women with prolonged use of paracetamol during pregnancy. The evidence for the association between paracetamol during pregnancy and autism spectrum disorder [ASD] and attention deficit hyperactivity disorder [ADHD] ismoderate.

Injection of **corticosteroids** may clinically enhance function after an acute muscle strain for limited period. Additional adjunctive treatments such as NSAIDs or paracetamol to enhance muscle healing and show promise but need additional data to better define their efficiency & efficacy and their side-effects.

**Side effects of corticosteroids** (that limit their medical use for athletes & bodybuilders) can occur with topical, ingested and injected steroids. However, most severe side effects come from oral steroids. Side effects from inhaled corticosteroids can include: cough, sore throat, difficulty in speaking, and minor nosebleeds. Topical corticosteroids can lead to thin skin, acne and red skin lesions. Injected corticosteroids can cause loss of skin color, insomnia, high blood sugar and facial flushing. Side effects from ingested steroids may include: acne, blurred vision, water retention, increased appetite and weight gain, stomach irritation, difficulty sleeping, mood changes and mood swings, glaucoma, thin and easy bruising skin, high blood pressure [**HBP**], muscle weakness, increased growth of body hair, susceptibility to infections, worsening of diabetes, delayed wound healing, stomach ulcers, Cushing syndrome, osteoporosis, depression and stunted growth in children.

**Side effects of NSAIDs**: Indigestion, including stomach aches, diarrhea, and stomach ulcers that can cause internal bleeding and anemia (extra medicine to protect your stomach may be prescribed to help reduce this risk), headaches, drowsiness, dizziness and allergic reactions. In rare cases, NSAIDs may cause problems in the liver, kidneys, heart and circulation, such as heart failure, heart attacks and sudden strokes.

**Opioid Analgesics**: Analgesic use by athletes is common. It has been observed that athletes used analgesics up to four times more often than their age-matched general population. Notably, **codeine** and **tramadol** are not included in the WADA list of prohibited substances in sport. Their use could be an attempt to compensate for fatigue, pain, and inflammation caused by injuries or overtraining. However, tramadol and codeine may have **side effects and health risks** such as: nausea, dizziness, drowsiness, and difficulty in concentrating. Scientific evidence regarding the impact of use and abuse on the sports population’s health is scarce, much less, with a sex- or gender-perspective. Athlete's use of codeine and tramadol have the potential abuse and opioid addiction.

No athlete, sportsman or bodybuilder is interested in such severe and life-threatening side effects from corticosteroids, opioids and NSAIDs.

**Green & safe alternative natural remedies for athletes**

Many athletes have turned recently to various dietetic interventions, including the use of **natural products** based on plants & fungi to avoid risk from synthetic drugs. Most herbs used in sports have a low to moderate effects on oxidative stress, fatigue resistance, endurance capacity, mental health and mood.

**Herbal medicines for sports**

The use of herbal medicinal products & supplements has increased during the last decade. Some herbs are used in sports to enhance muscle mass and strength, increase fat burning metabolism and energy maintenance and to protect from oxidative damage.

Plant secondary metabolites (alkaloids, terpenes, flavonoids, saponins & phenols) have important biological properties: anti-allergic, anti-inflammatory, anti-microbial (bacteria, fungi & viruses), anti-carcinogenic, hepato-protective, cardio-protective, anti-thrombotic and vasodilator actions. These biological properties are mediated by their **antioxidant** characteristics and **redox** actions. Exercise induced oxidative stress is caused by peroxides and reactive oxygen (free radical) species [**ROS**] produced during extensive muscle training. Antioxidants neutralize ROS and scavenge as well as decompose peroxides and reactive hydroxyls.

*Panax Ginseng* [**Ginsenosides**]*, Coffea Arabica, Guarana, Yerba Mate, Green Tea, Cola nut* [**Caffeine**]*, Theobroma Cacao* [**Theobromine**]*. Ephedra* [**Ephedrine**]*, Ginger* [**Ginerol**]*, Tribulus Terrestis* [**Dioscine,** Diosgenin & Protodioscin]*, Rhodola Rosea, Ginko biloba, Cayene, Arnica, Garlic, Licorice, Curcuma longa, Echinacea, Astragals, Salix alba, Saffron, Fenugreek, Myrtus Communis,* *Cordyceps Sinensis* {Fungus}*,* and raw, organic *Broccoli* sprouts [**sulphoraphanine 🡪 sulphoraphan**]. Sulphoraphan induces cellular production of Glutathione – the main antioxidant molecule in our body.

Herbal supplements activate the central nervous system [**CNS**] via stimulation of catechol amines [**CAs**]. CAs was recently found to increase both anaerobic & aerobic performances in athletes.

Small amounts of Caffeine & Ephedrine were found to enhance muscle strength and increase body mass in trained individuals. Caffeine is a potent adenosine antagonist which increases many neurotransmitters [**NTs**] activities. Caffeine ingestion was found to improve maximal blood lactate and free fatty acid concentrations in athletes and improves mental alertness. Ephedrine is an alkaloid with ergogenic (enhance physical performance, stamina, or recovery) properties that enhance physical performances and reduces fatigue. Ephedrine is used medically as stimulant to treat low blood pressure, urinary incontinence, narcolepsy, asthma and depression. Ephedrine was recently found to increase muscle performances in athletes.

Theobromine & Theophylline alkaloids possess antioxidant properties and increase energy expenditure by stimulating brown adipose tissue thermogenesis.

*Ginseng* root have great effect on the CNS and appears to increase alertness and to speed-up reaction time. Active phytochemicals from *Ginseng* root (alkaloids & saponin steroids) are strong antioxidants and anti-inflammatory agents that stimulate steroid hormone [Cortisol] production in the body. Ginseng root extract have beneficial effects on the adrenal glands, sexual functions, as well as cognitive and anaerobic performances in athletes. Ginseng also improves alertness and fatigue resistance in athletes.

*Tribulus Terrestris* contains the **steroid** **Saponins** (Dioscine) that have beneficial effects on libido, cardiovascular system and physical fitness. *Terrestris* extract improves Testosterone production in males, enhancesmuscle growthand reduce inflammation.

*Rhodiola* *cremulata* and *Astragalus* help relieve muscle, bone & joint pain and enhances aerobic performances in athletes.

*Ginger* (*Zingiber officinale*) root is listed in the FDA's "safe list". It contains **Gingerols** that have strong anti-inflammatory and analgesic effects. Ginger also cause fatigue resistance in athletes.

*Curcuma* root contains the diaryl heptanoid - **Curcumin** and phenols that reduce serum inflammation markers, such as creatine kinase [**CK**].

*Cordiceps Sinensis* fungus has been demonstrated an efficient role for the treatment of **high** **cholesterol** blood levels, **high** **blood pressure** and immune disorders. *Cordiceps* fungi ingestion also induces higher endurance performances in athletes.

However, despite their general positive effects, these herbs should be used with precaution because high doses may cause **harmful side effects** on kidney, liver, thyroid, pancreas and stomach. Some may cause insomnia, headaches, confusion, irritation, anxiety, nausea, diarrhea & blood pressure fluctuations. Some herbal medicines can interfere with medications such as steroids, anticoagulants & enzyme inhibitors.

Moreover, Ephedrine and its derivatives (Cathine, Methylephedrine & Pseudoephedrine) are considered to be prohibited **doping substances**.

**Endocannabinoids [eCBs] deficiency syndrome [EDS]**

There are a number of conditions the medical world currently has no explanation for, and that appears to be ‘treatment resistant’. These are by no means rare, either, with the likes of: endometriosis, fibromyalgia, migraines and inflammatory bowel disease [**IBD**] affecting millions all over the world. An eCBs deficiency (where the endocannabinoid system [**ECS**] doesn’t produce enough eCBs – the lipid mediators (the NTs it is activated by) - might be the root cause of many different disorders called EDS. The ECS affects our physical and mental well-being, adapting to health conditions and environmental changes as needed.

Imbalanced ECS increases the risk of many diseases: Epilepsy, anxiety, migraine,, fibromyalgia, MS, IBD, digestive disorders, brain, breast & prostate tumors, osteoarthritis, rheumatic arthritis, endometriosis & dermatitis, to name only a few. Interestingly, some herbs & spices such as: *Turmeric*, *Black pepper*, *Echinacea*, *Saffron, Cloves* *, Humulus lupulus* [Hops]*,* and *Cannabis sativa* are known to support the ECS.

**Full-spectrum** ***Cannabis* oil** provides nutrients for the ECS and help filling the gaps due to EDS.

**Cannabinoids from *Cannabis***

The *Cannabis Sativa* L. plant was originated in the high north-eastern Tibetan Plateau about 27.8 million years ago. The human cultivation started in East China about 12,000 years ago, as one of the 1st domesticated plants during early Neolitic times. The first ritual use of *Cannabis* happened in a Jewish temple in Israel, dating about 2,700 years ago. This annual dioecious plant belongs to the Cannabaceae family and its inflorescences contain most of the active compounds in glandular trichomes [**GTs**]. Mature female flowers develop large amounts of resin with a high content of cannabinoids, flavonoids, terpenes and more.

**Cannabinoid biosynthesis** begins with the precursor molecules olivetolic acid [**OLA**] and geranyl pyrophosphate [**GPP**], which combine to form cannabigerolic acid [**CBGA**] that serves as the precursor molecule to all other pCBs and is converted enzymatically to THCA, CBDA or CBCA inside glandular trichomes [**GTs**] in the mature female plant flowers (inflorescences). Strains with reduced activity of the 3 synthesis enzymes can accumulate higher levels (up to 100%) of CBGA. All pCBs are produced as their acidic form and are then decarboxylated by heat or aging to create the neutral active form.

*Cannabis* is a complex, polymorphic plant species, which produces a vast array of different bioactive metabolites (about 500), the three major chemical groups being: phytocannabinoids [**pCBs**], terpenoids and flavonoids. The term ‘pCBs’ (plant-based cannabinoids) refers to a group of lipophilic and pharmacologically active, oxygenated C19-22 aromatic hydrocarbon, terpeno-phenolic compounds found in the leaves and flowers of the *Cannabis* plant The pCBs are synthesized by the plant in their **acidic form** that undergoes non-enzymatic **de**carboxylation upon heating or ageing, in the plant and after harvesting. The psychoactive cannabinoid - tetrahydrocannabinol (Δ- 9 -**THC**) and the non-psychoactive cannabidiol (CB**D**), are the two major cannabinoids that have been studied in details.

**Δ9-THC** is responsible (although not the only one pCB) for the **psychoactive effect** of the *Cannabis* plant. This occurs only for the decarboxylated compound since it must get through the hematoencephalic barrier (HEB) to reach the CB1 receptors in the CNS that mediate this effect. Other major cannabinoids are cannabinol [CB**N**], which is the oxidative degradation product of Δ9-THC, CB**D** and cannabigerol [CB**G]**. The interaction of agonists with CB1 receptors is also responsible for the analgesic effect of some pCBs. This cannabinoid participation in the **nociceptive transmission** has been intensively investigated. On the other hand, CB**D** does not have psycho-activity since it has very low or no affinity for the cannabinoid receptors ortho-steric site. CB**D** also shows antioxidant and anti-inflammatory activities, and antimicrobial, anxiolytic and anticonvulsant properties. The immune-modulatory activity of THC is related to the affinity with CB**2** receptors that are highly expressed in the immune system. In addition, CB2 receptors are also considered to be involved in neuro-inflammation, atherosclerosis and **bone re-modeling**. Cannabinoids are generally active in various non-cannabinoid receptors, which explains the variety of pharmacologically recognized actions and those that have not yet been investigated. Recently, many studies learn about how cannabinoids and the broader ECS help **maintain homeostasis** in the whole body and affect physical health in myriad ways. This vast system of cellular receptors, ligands (compounds {**a**gonists or **anta**gonists} that bind to these receptors), transporters and enzymes (that synthesize or degrade eCBs) also influences mental health, cognition, emotion, motivation and other processes. Increased ECS activity was found to improve **social interaction** and **motivation**. Using a monoglycerol lipase [**MAGL**] inhibitor (the enzyme that degrades 2-AG), that boosts levels of that eCB in the whole body, was found to facilitate **goal seeking** in mice.

**The ECS – The eCBs and their Receptors**

Anandamide = arachidonyl ethanol amine [**AEA**] and 2-arachidonyl glycerol [**2-AG**] both bind with high affinity as full (2-AG) or partial (AEA) agonists to both CB1 & CB2 receptors. The *Cannabis* plant pCB, delta-9-tetrahydrocannabinol [**THC**] is a very high affinity partial agonists of both ECS receptors. THC produces euphoria and stimulates appetite. AEA also enhances pleasure and motivation, regulates appetite & sleep and alleviates pain. Cannabidiol [CB**D**] is non-euphorigenic and has antiepileptic and anti-inflammatory effects. CBD does **not** bind ECS receptors at all. Interestingly, cannabigerol [CB**G**] exhibits affinity and activity characteristic between THC & CBD.

**Cannabinoid receptor type 1** (**CB1**) is the most abundant G protein-coupled receptor [**GPCR**] throughout the CNS. The broader family of GPCRs includes roughly 750 different receptors, nearly 150 of which are targeted by pharmaceuticals representing more than one-third of all approved drugs in the USA & Europe. CB1 is present in very high levels in several brain regions, including the cerebellum and the hippocampus, and is distributed at lower levels more generally, where it helps modulating NT (the excitatory glutamate [**Glu**] and the relaxing gamma-aminobutyric acid **[GABA]**) release. **γ-aminobutyric acid** is the chief inhibitory NT in the mature mammalian CNS. Its principal role is reducing neuronal excitability throughout the nervous system. **Glutamic acid** [**Glu**], or the ionic form is known as glutamate, is an α-amino acid that is used by almost all living beings in the biosynthesis of proteins. It is non-essential in humans, meaning that the body can synthesize it. It is also an abundant excitatory NT in the vertebrate nervous system. Interestingly, Glu also serves as the precursor for the synthesis of the inhibitory GABA in GABA-ergic neurons.

Key **CB1 agonists**, which activate the receptor to produce a variety of cellular responses, include the eCBs - **anandamide** (**AEA**) & **2-arachidonyl glycerol** (**2-AG**) and the pCB - **THC**. So it’s really no wonder that *cannabis*, as well as various foods & medicinal herbs that enhance the ECS, can have a pronounced, positive impact on brain function. Cannabinoid compounds bind and activate ECS receptors – CB1 (in the brain) and CB2 (in the periphery & immune system cells).

Interestingly, the affinity of the pCB - THC to CB**1** is 6-8 times higher compared to the eCBs – 2-AG & AEA, respectively, and its affinity to CB**2** is 6-15 times higher compared to 2-AG & AEA, respectively.

**Mitochondria**l **CB1R** [**mCB1R**] Mitochondria are found in every complex organism and they produce around 90% of the energy we need to survive. They also play a vital role in killing cells appropriately (to avoid tumor growth), produce chemicals we need and get rid of stuff we don’t. In short, they are majorly important and if they stop working properly, very bad things happen to our body .There are membrane eCB receptors in the very structure of mitochondrial cell walls [mCB1R], meaning that a fully functioning ECS is needed to support these receptors and keep the very fabric of our being going strong. Functioning mitochondria is most important for athletes, sportsman & body builders.

**Cannabinoid receptor type 2 (CB2)** is a GPCR from the cannabinoid receptor family that is closely related to the CB1 receptor, which is largely responsible for the efficacy of endocannabinoid (eCB)-mediated **pre**synaptic-inhibition, the psychoactive properties of THC and some other pCBs such as CBG. The principal endogenous ligand (high-affinity **full** agonist) for the CB2 receptor is 2-AG.

The CB2 receptor is comprised by approximately 360 amino acids [**AAs**], making it shorter than the 473-amino-acid-long CB1 receptor. As is commonly seen in GPCRs, the CB2 receptor has seven trans-membrane [**7-TM**] panning domains, a glycosylated N-terminus, and an intracellular C-terminus. The C-terminus of CB2 receptors appears to play a critical role in the regulation of ligand-induced receptor **de**sensitization and down-regulation following repeated agonist application, perhaps causing the receptor to become less responsive to particular ligands. The human CB1 and the CB2 receptors possess approximately 44% AA similarity. When only the trans-membrane regions of the receptors are considered, however, the AA similarity between the two receptor subtypes is approximately 68%. The AA sequence of the CB2 receptor is less highly conserved across human and rodent species as compared to AA sequence of the CB1 receptor. Based on computer modeling, ligand interactions with CB2 receptor residues S (Serine) 3.31 and F (Phenylalanine) 5.46 appears to determine differences between CB1 and **CB2 receptor selectivity**. In CB2 receptors, lipophilic groups interact with the F5.46 residue, allowing them to form a hydrogen bond with the S3.31 residue. These interactions induce a conformational change in the receptor structure, which triggers the activation of various intracellular signaling pathways. Like the CB1 receptors, CB2 receptors inhibit the activity of adenylyl cyclase [**AC**] through their Gi/Goα subunits. CB2 can also couple to stimulatory Gαs subunits leading to an increase of intracellular cyclic adenosine monophosphate [**cAMP**], as has been shown for human leukocytes. Through their Gβγ subunits, CB2 receptors are also known to be coupled to the MAPK-ERK pathway, a complex and highly conserved signal transduction pathway, which regulates a number of cellular processes in mature and developing tissues. Activation of the MAPK-ERK pathway by CB2 receptor agonists, acting through the Gβγ subunit, ultimately results in changes in cell migration. Five recognized cannabinoids are produced endogenously: AEA, 2-AG, 2-arachidonyl glyceryl ether (noladin ether), virodhamine, and N-arachidonoyl-dopamine (NADA). Many of these ligands appear to exhibit properties of functional selectivity at the CB2 receptor: 2-AG activates the MAPK-ERK pathway, while noladin ether inhibits AC. Primary research on the functioning of the CB2 receptor has focused on the receptor's effects on the immunological activity of leukocytes. This receptor has been implicated in a variety of modulatory functions, including immune suppression, induction of apoptosis, and induction of cell migration. CB2 also signals via Gαs and increases intracellular cAMP in human leukocytes, leading to induction of the cytokines - interleukin 6 [IL-6] and IL-10 release. Although the exact role of the cAMP cascade in the regulation of immune responses is currently under debate, laboratories have previously demonstrated that inhibition of AC by CB2 receptor agonists results in a reduction in the binding of transcription factor - cAMP response element-binding protein [**CREB]** to the DNA. This reduction causes changes in the expression of critical immune-regulatory genes and ultimately suppression of eccessive immune function. Later studies examining the effect of synthetic cannabinoid agonist JWH-015 on CB2 receptors revealed that changes in cAMP levels result in the phosphorylation of leukocyte receptor tyrosine kinase at Tyr-505, leading to an inhibition of T cell receptor signaling. Thus, CB2 agonists may also be useful for treatment of **inflammation** and **pain**, and are currently being investigated, in particular for forms of pain that do not respond well to conventional treatments, such as neuropathic pain. Consistent with these findings are studies that demonstrate increased CB2 receptor expression in the spinal cord, dorsal root ganglion, and activated microglia [**MG**] in the rodent neuropathic pain model, as well as on human hepto-cellular carcinoma tumor samples. CB2 receptors may have possible therapeutic roles in the treatment of many neurodegenerative disorders such as Alzheimer's disease [**AD**]. Specifically, the high affinity CB2 synthetic agonist JWH-015 was shown to induce macrophages to remove native beta-amyloid protein from frozen human tissues. In patients with AD, beta-amyloid proteins form aggregates known as senile plaques, which disrupt neural functioning. Changes in eCBs levels and/or CB2 receptor expressions have been reported in almost all diseases affecting humans, ranging from psychiatric, cardiovascular, GI, liver, kidney, neurodegenerative, **bone, muscle, joint,** skin, autoimmune, lung disorders to pain and cancer. The prevalence of this trend suggests that modulating CB2 receptor activity by either selective CB2 receptor agonists or inverse agonists/antagonists depending on the disease and its progression holds unique therapeutic potential for these pathologies.

Finally, we have reached the main subject of this review...

**Cannabigerol**

Cannabigerol [**CBG**] was discovered in 1964 by Dr. Yehiel Gaoni and Dr. Raphael Mechoulam in Israel and has shown a wide range of medicinal efficacy. This includes research indicating that it may be effective in the treatment of bladder dysfunction, cancer in general, colorectal cancer [**CRC**] in particular, glaucoma, Huntington disease [**HD**], Parkinson disease [**PD**], Alzheimer disease [**AD**], multiple sclerosis [**MS**], , glaucoma, psoriasis, immune dysfunction, bladder diseases and inflammatory bowel disease [**IBD**]. CBG was found to reduce intestinal inflammation and the production of nitric oxide [**NO**]. It also reduces the formation of reactive oxygen species [**ROS**] in the intestine.

CBG is called the “Stem cell cannabinoid” or “mother of all cannabinoids”, because it is the single original cannabinoid produced early in the *Cannabis* plant’s growth cycle, from which all other pCBs are then synthesized through different enzymatic metabolic processes as the plant matures. Like THC, CBD and CBC, CBG exists in the raw *Cannabis* plant in its acidic form, **CBGA**, until it is heated and converts to CBG. CBG is non-intoxicating and safe on consumption much like CB**D**, due to the fact that both molecules work **in**directly on neurological pathways, rather than directly binding to the CNS's CB1 receptors of the ECS like the "high"-inducing, euphoric Delta-9-THC.

Of several cannabinoids tested, CB**G** had the strongest potency to inhibit **platelet aggregation**.

In biochemistry and pharmacology, a variety of parameters are reported as measures of the **potency** of enzyme/receptor inhibitor/agonist drugs, including *K*i, *K*d, IC50 & EC50 (in nM). **Ki** refers to inhibition constant, while **Kd** means dissociation constant. Both terms are used to describe the **binding affinity** that a small molecule has for an enzyme or receptor. The difference is that Kd is a more general, all-encompassing term. Kd measures the equilibrium between the ligand-protein complex and the dissociated components.

CBG, has a relatively weak competitive partial agonistic effect at CB**1** (Ki 440 or 1,045 nM) and CB**2** (Ki 337 or 1,225 nM). Because of its low cannabinoid receptor potency, it can functionally antagonize the CB1 effects of THC.

CBG may stimulate a range of receptors important for **pain**, **inflammation**, and **heat sensitization**. This compound can stimulate TRPV1, TRPV2, TRPA1, TRPV3, TRPV4, and α2-adrenoceptor activity. It is a relatively potent TRPM8 antagonist for possible application in prostate cancer and over-activity as well as bladder pain. CBG can also antagonize the stimulation of serotonin 5-HT1A and CB1 receptors with significant efficiency. Older work supports gamma aminobutyric acid (**GABA**) uptake inhibition greater than THC or CBD that could suggest **muscle relaxant** properties. CBG have **analgesic** and anti-erythemic effects and its ability to block lipooxygenase [**LOX**] were said to surpass those of THC. CBG also demonstrated modest antifungal effects. CBG has remarkable anticancer properties; it has proved to be an effective cytotoxic in high dosage on human epithelioid carcinoma and is one of the more effective pCBs against breast & colon cancers. CBG has significant **antidepressant** effects in rodents and is a mildly **antihypertensive** agent. Additionally, CBG inhibits keratinocyte proliferation suggesting utility in psoriasis. CBG is a strong AEA uptake inhibitor and a powerful agent against MRSA (methicillin-resistant *Staphylococcus aureus*) bacteria. CBG behaves as a potent α2-adrenoreceptor agonist, supporting **analgesic** effects previously noted, and moderate 5-HT1A antagonist suggesting **antidepressant** properties.

**Effects on the alpha-2 Adrenergic Receptor (adrenoceptor) [α-2AR]:**

THC is known for increasing blood pressure but when researchers use smaller doses they see a different response. Other cannabinoids such as CBD and CBG rapidly decrease inflammation and fight the effects of cardiovascular diseases such as swelling and fluid retention often accompany such health conditions. Recent research obtained evidence from in vitro experiments that CBG is a very potent α2-adrenoceptor agonist. This was unexpected as the structure of this pCB is unlike that of any established α2-adrenoceptor ligands and as no other cannabinoid has been reported to behave in this way. Activation of alpha-2 adrenoceptor suppresses the release of norepinephrine [**NE**] by negative feedback mechanism, causes vasoconstriction of arteries (such as coronary arteries), veno-constriction of veins, inhibition of lipolysis, sedation, analgesia and facilitating of **cognitive functions** associated with the prefrontal cortex [**PFC**] such as working memory, attention & executive functioning. By increasing NE secretion in the brain, CBG can treat depression. By enhancing sympathetic nervous system activity, alpha-2AR agonist, such as CBG, can reduce high blood pressure [**HBP**].

Actions of alpha-2 AR include: Decreased insulin and increased glucagon release from the pancreas. Increased platelet aggregation and decreased peripheral vascular resistance. CBG can also block 5-HT**1A** and cannabinoid CB**1** receptors albeit with potency much lower than that with which it appears to activate **α2**-ARs. All these physiologic effects of CBG are very important for athletes.

**Effects on the Serotonin 5-HT1A Receptor:**

Serotonin [**5-hydroxy tryptamine (5-HT)**] is a monoamine NT produced throughout the body for many physiologic and neurologic functions. It plays a central role in maintaining homeostasis (such as enteric GI nervous system). In the CNS, serotonin is a target of many anti-depression medications. 5-HT binds to different serotonin receptor families. The 5-HT1A receptor interacts with both eCBS & pCBs. It is a Gi/o GPCR that inhibits adenylate cyclase [**AC**] activity and interact with various growth factors [**GFs**] pathways. It is located both pre- and post-sinapticallly and the downstream functions of this receptor activation vary based on neuronal density & function. Inhibition of pre-synaptic 5-HT1A receptor affects the efficacy of other 5-HT-modulating drugs such as selective serotonin reuptake inhibitors [**SSRIs**]. 5-HT1A antagonists reduce the increase in that receptor activity created by antidepressants which increase synaptic 5-HT availability. As a potent 5-HT1A receptor antagonist, CBG can be used to treat major depressive disorder [**MDD**]. Recently, CB**G** & CB**D** were found to have neuro-protective effects against oxidative neurotoxicity through 5-HT1A receptor mediated mechanism. The severe side effects of SSRIs and their addictive nature as well as the rapid development of tolerance to their anti-depressant effects, paved the way to consider safe & natural remedy to treat chronic depression - such as CBG alone or together with CBD.

**Effects on the Peroxisome Proliferator-Activated Receptors [PPARs]**

PPARs are a family of nuclear receptors [**NRs**] transcription factors [**TFs**] that as a result of their nuclear activation by agonists, conformational chances are induced and binding of PPARs to response elements of DNA modulate gene expression. The 3 PPARs isoforms in the human body are: alpha, beta & gamma. These receptors transcriptionally regulate **lipid & glucose metabolism**, hepatic metabolic functions, blood fatty acid levels and inflammation. PPARs accept a wide variety of ligands because of their large binding domains. Many eCBs & pCBs interact with the various PPARs isoforms. CBG exhibits stronger affinity to the PPAR-γ receptor compared to CBD & THC. PPAR-γ regulates adipocyte differentiation, insulin sensitivity and inflammation. Activation of this nuclear receptor by CBG can treat symptoms in patients suffering from type-2 diabetes. Both THC, CBD & CBG are PPAR-γ agonists whereas, AEA is a dual agonist of PPAR alpha & gamma. Recent study identified CBG, CBGA, & CBDA as PPARα/γ isoforms **dual agonists.** Dual PPAR agonists effect downstream gene transcription in hepatocytes & adipocytes that is most important for bodybuilders & athletes.

**Therapeutic Potential of CBG**

As CBG is not psychoactive, it is currently marketed **legally** in many countries as dietary supplement. CBG have **good safety profile** in humans and has been demonstrated to have a wide array of medical applications. CBG is anti-inflammatory, anti-malignant, anti-bacterial, neuro-protectant, vasoconstrictor, muscle relaxant & pain relieve natural and remedy that many athletes learnt to appreciate lately.

**Gamma amino butyric acid [GABA] reuptake inhibition**

CBG was found to inhibit GABA reuptake in the brain & periphery. When GABA uptake is inhibited, you actually have **muscle relaxation** and **anti-anxiety** effects, so CBG appears to promote similar effects that CBD has. CBG also appears to have **anti-depressant** properties.

**Anti-microbial action:**

Antibiotic resistance in bacteria is a growing healthcare issue.

Most pCBs have strong anti-bacterial effects on Gram-positive bacteria. The outer lipopolysaccharide [**LPS**] coat (envelope) of Gram-negative bacteria protects them from the action of pCBs on their membranes. Like many *cannabis* compounds, CBG have **anti-microbial** benefits, including anti-fungal action and bacteria killing qualities, particularly against the **antibiotic [Methicillin]-resistant *Staphylococcus a*ureus** [**MRSA**] infection. MRSA refers to a group of Gram-positive bacteria that are genetically distinct from other strains of *Staphylococcus aureus.* It is responsible for several difficult-to-treat infections in humans. MRSA is any strain of *S. aureus* that has developed (through natural selection) or acquired (through horizontal gene transfer) a multiple drug resistance to beta-lactam antibiotics. β-lactam antibiotics are a broad-spectrum group that include some penams (**penicillin derivatives** such as methicillin and oxacillin) and cephems, such as the cephalosporins. Strains able to resist these antibiotics are classified as MRSA. MRSA is common in hospitals, prisons, nursing homes and sport resorts where people with open wounds, invasive devices such as catheters, and weakened immune systems are at greater risk of hospital-acquired infection. Locker rooms, gyms, and related athletic facilities offer potential sites for MRSA contamination and infection. Recent study found that CBG, CBC, CBD, and THC are all particularly effective against this bacterial infection. Recent study found that CBG inhibit enoyl acyl carrier protein reductase in bacteria. Inhibition of bacterial fatty acid metabolism contributes to the anti-bacterial actions of CBG.

**CBG against oral *Streptococcus mutans:*** Bacteria belonging to the genus *Streptococcus* are the first inhabitants of the oral cavity, which can be acquired right after birth and thus play an important role in the formation of the oral microbiota. In the oral cavity, many microorganisms have been found among them *S. mutans* is considered the most cariogenic bacteria. Therefore, the inhibition of *S. mutans* is a key objective in the prevention of dental caries (tooth decay). Recent study demonstrates an anti-bacterial effect of the *Cannabis* component CBG toward the cariogenic bacteria S. mutans. CBG acts at several levels: It exerts a bacteriostatic effect that is affected by the initial bacterial cell density. It affects the membrane structure and causes intracellular accumulation of mesosomes. It causes immediate membrane hyperpolarization, reduces the membrane fluidity, increases the membrane permeability and prevents the drop in pH caused by *S. mutans*, thereby preventing its cariogenic property. The interference of CBG with the caries causative *S. mutans* may provide a novel innovative way to combat dental caries.CBG alters the bacterial membrane properties, induces membrane hyperpolarization and decreases the membrane fluidity. CBG-treated bacteria showed increased propidium iodide [PI] uptake and reduced calcein AM staining, suggesting that CBG increases the membrane permeability & reduces its metabolic activity.

**Neurological & Neuro-protective effects:**

CBG have therapeutic potential in healing various **neurologic disorders**.

CBG has also been found to work as a neuro-protectant (a compound that prevents the degeneration of brain and nerve tissue) leading scientists to test it against the debilitating Huntington’s disease [**HD**] and several other neurodegenerative diseases. Through chemical pathways similar to CBD, CBG is able to **dull** perceptions of pain**,** to provide both **anti-inflammatory** and **pain relieving** benefits for those suffering from chronic pain and inflammatory conditions (like arthritis) and muscle, bone & joint pain of athletes. CBG improves motor deficits and preserve neurons against nitroproprionic acid toxicity. CBG is also able to **inhibit the reuptake** of the “bliss molecule” **anandamide** which provides a range of benefits including **mood elevation**, **anxiety relief** (even anxiety from too much THC consumption), **muscle relaxation**, and **seizure relief**.

**Anti-Cancer effects:**

Like other pCBs, there is some early science suggesting that CBG can have **anti-cancer** potential by destroying the cells of several aggressive cancer types, including colon, prostate and breast cancers, with no negative effects on healthy, non-malignant cells. CBG is also able to increase the entourage effect and allow more medical benefit from **whole-plant** cannabis medicine. CBG was found to promote apoptosis, stimulate ROS production, up-regulate CHOP mRNA and reduce cell growth in colorectal cancer cells [**CRCs**]. CBG effect on cell growth was **in**dependent from transient potential receptors [**TRPs**] TRPA1, TRPV1 and TRPV2 ion channels activation, was further increased by a CB**2** receptor antagonist, and mimicked by other TRPM8 channel blockers but not by a 5-HT1A antagonists. Furthermore, the effect of CBG on cell growth and on CHOP mRNA expression was reduced in TRP**M8** silenced cells. In vivo, CBG inhibited the growth of xenograft tumors as well as chemically-induced colon carcinogenesis. CBG hampers colon cancer progression in vivo and selectively inhibits the growth of CRCs, an effect shared by other TRP**M8** antagonists. CBG, that acts as a specific TRPM8 antagonist should be considered in CRC prevention and cure.

**Anti-inflammatory effects:**

CBG & CBGA had demonstrated effects that mimic the **inflammatory pain relief** of common NSAID pain relievers (like Acetaminophen, Ibuprofen, and Aspirin) - however, it does not degrade the stomach lining like NSAIDs do, making CBG & CBGA a potentially safer treatment for pain & inflammation than these traditional pharmaceuticals.

**Inhibition of cyclooxygenases [COX-1 & COX-2]:** Cyclooxygenase or prostaglandin endoperoxidse symtase (**PTGS**) is the enzyme that produces prostanoids such as thromboxane & prostaglandins from arachidonic acid [**AA**]. The specific reaction catalyzed is the conversion from AA to Prostaglandin H2, via a short-living Prostaglandin G2 intermediate. A favorable steric interaction of CB**G** inside COX-2 binding pocket was recently observed. Pre-clinical studies suggest more diverse uses for CBG as a COX-2 inhibitor, similar to the popular group of pharmaceuticals known as non-steroidal anti-inflammatory drugs (NSAIDs). In one study, CBG, THC and CBD all appeared to inhibit COX-2 enzymes, although higher concentrations were required compared to traditional NSAIDs. Still, NSAIDs come with a number of severe side effects that cannabis-based medicines do not.

Culinary mushrooms, like *Maitake*, may be able to partially inhibit COX-1 and COX-2. A variety of flavonoids have been found to inhibit COX-2.

Fish oils provide alternative fatty acids to AA. These acids can be turned into some anti-inflammatory prostacyclins by COX enzymes instead of pro-inflammatory prostaglandins.

**Hyperforin** from *Hypericum perforatum* (St John's wort) has been shown to inhibit COX-1 around 18 times as much as Aspirin. Hyperforin is a phytochemical produced by some of the members of the plant genus Hypericum and it may be involved in the pharmacological effects of the herb specifically in its **antidepressant** effects. Hyperforin may be a constituent responsible for the antidepressant and anxiolytic properties of the extracts of St. John's wort. In vitro, it acted as a reuptake inhibitor of monoamines, including serotonin [**5-HT**], norepinephrine [**NE**], dopamine [**DA**], **GABA** and **Glu**, with IC50 values of 0.05-0.10 μg/mL for all compounds, with the exception of Glu, which is in the 0.5 μg/mL ranges. In other studies, hyperforin was found to induce cytochrome P450 enzymes CYP**3A4** and CYP**2C9** activity by binding to and activating the pregnane X receptor [**PXR**]. PXR, also known as the steroid and xenobiotic **sensing** **nuclear receptor** (**SXR**) or nuclear receptor subfamily 1, group I, member 2 (**NR1I2**), is a nuclear receptor protein whose primary function is to sense the presence of foreign toxic substances and in response up regulate the expression of proteins involved in the detoxification and clearance of these substances from the body. PXR belongs to the nuclear receptor superfamily, members of which are **transcription factors** characterized by a ligand-binding domain and a DNA-binding domain. PXR is a transcriptional regulator of the cytochrome P450 gene CYP3A4, binding to the response element of the CYP3A4 promoter as a heterodimer with the 9-cis **r**etinoic acid **r**eceptor [**RXR**]. PXR is activated by a range of compounds that induce CYP3A4, including the corticosteroid dexamethasone and the antibiotic rifampicin. Meta-analyses of preliminary clinical trials evaluating the efficacy of St. John's wort herb for treating mild-to-moderate depression indicated a response similar to SSRIs and with better tolerance, although the long-term generalization of study results was limited by the short duration (4–12 weeks) of reviewed studies. Calcitriol (**vitamin D**) significantly inhibits the expression of the COX-2 gene. Interestingly, **CBGA** was found to inhibit both COX-1 & COX-2 iso-zymes.

**Analgesic effects:**

CBG acts as an anti-inflammatory, anti-bacterial agent that also **regulates mood** and **mitigates** **pain**. CBG is unique in its interactions with alpha-2 adrenoceptor [**α-2 AR**] and serotonin (5-hydroxytryptamine) (**5-HT 1A**) receptors. Recent studies revealed that CBG's pharmacology addresses therapeutic targets distinct from those of THC & CB**D**. It activates alpha-2 adrenoceptor, CB**2**R, peroxisome proliferator-activating receptor [**PPAR -γ**] and most transient receptor potential ion channel [**TRPs**]. Interestingly, CBG is a potent agonist of all TRPs accepts TRP**M8** (the cold & menthol receptor) at which it acts as an antagonist. CBG also antagonizes CB**1**R, 5-HT**1A**R, and the sodium channel [**NAV**]. These antagonistic effects may contribute to CBG's anti-malignant & analgesic actions.

**Effects on transient receptor potential ion channels [TRPs]:**

TRP channels are a group of ion channels located mostly on the plasma membrane of numerous animal cell types. Most of these are grouped into two broad groups: Group 1 includes TRP**C** ("C" for canonical), TRP**V** ("V" for vanilloid), TRP**M** ("M" for melastatin), TRP**S** ("S" for soromelastatin), TRP**N** ("N" for no mechanoreceptor potential C), and TRP**A** ("A" for ankyrin). Group 2 consists of TRP**P** ("P" for polycystic) and TRP**ML** ("ML" for mucolipin). Many of these channels mediate a variety of sensations such as **pain**, temperature, tastes, pressure, and vision. In the body, some TRP channels are thought to behave like microscopic thermometers and used to sense hot or cold. Some TPPs act as sensors of osmotic pressure, volume, stretch, and vibration. Most of the TPRs are activated or inhibited by **signaling lipids** and contribute to a family of lipid-gated ion channels. These ion channels have a relatively non-selective permeability to cations, including sodium, calcium and magnesium. Some TRP channels are activated by molecules found in spices like *garlic* (allicin), *chili pepper* (capsaicin), *wasabi* (allyl isothiocyanate) and others are activated by menthol, camphor, peppermint, stevia & cooling agents. Some TPRs are activated by molecules found in *cannabis* (THC, CBD, **CBG**, CBC and CBN).

The effects of 11 pure cannabinoids and botanical extracts [botanical drug substance (**BDS**)] from Cannabis varieties selected to contain a more abundant pCBs, on TRPV1, TRPV2, TRPM8, TRPA1, human recombinant diacylglycerol lipase α (**DAGL**α), rat brain fatty acid amide hydrolase (**FAAH**), COS cell monoacylglycerol lipase (**MAGL**), human recombinant N-acylethanolamine acid amide hydrolase (**NAAA**) and anandamide cellular uptake by RBL-2H3 cells, were studied using fluorescence-based calcium assays in transfected cells and radiolabelled substrate-based enzymatic assays. Cannabinol (CB**N**), cannabichromene (CB**C**), the acids (CB**DA**, CB**GA**, THC**A**) and propyl homologues (CBD**V**, CBG**V**, THC**V**) of CBD, cannabigerol (CB**G**) and THC, and tetrahydrocannabivarin acid (THC**VA**) were also tested. CBD, CB**G**, CBGV and THCV stimulated and **de**sensitized human TRP**V1**. CBC, CBD and CBN were potent rat TRP**A1** agonists and desensitizers, but THCV-BDS was the most potent compound at this target. **CBG-BDS** and THCV-BDS were the most potent rat TRP**M8** antagonists. All non-acid cannabinoids, except CBC and CBN, potently activated and desensitized rat TRP**V2**. CB**DV** and all the acids inhibited DAGLα (the enzyme that produces 2-AG). Some BDS, but not the pure compounds, inhibited MAGL (the enzyme that degrades 2-AG). CBD was the only compound to inhibit FAAH (the enzyme that degrades AEA), whereas the BDS of CBC > CBG > CBGV inhibited NAAA (the enzyme that produces AEA). CBC = CB**G** > CBD inhibited AEA uptake, as did the BDS of THCVA, CBGV, CBDA & THCA.

**Effects on Bones:**

As we age, our bones become thinner, we suffer fractures more often, and bone-diseases such as osteoporosis are more likely to occur. One responsible mechanism involves the impaired function of the bone-marrow stem cells, which are required for the maintenance of bone integrity. Recent researche have now shown that the reduced stem cell function upon aging is due to changes in their epigenome. As a result of CB**2** activation, CBG stimulate bone growth. Athletes need much support for bone maintenance & growth and can get much benefit from the consumption of CBG in oral tinctures.

**Bladder dysfunction treatment:**

Voiding of the bladder is the result of a parasympathetic muscarinic receptor activation of the detrusor smooth muscle. However, the maintenance of continence and a normal bladder micturition cycle involves a complex interaction of cholinergic, adrenergic and peptidergic systems. The cholinergic component of bladder control involves two systems, acetylcholine (**ACh**) released from parasympathetic nerves and from non-neuronal cells within the urothelium. The actions of ACh on the bladder depend on the presence of muscarinic receptors that are located on the detrusor smooth muscle, where they cause direct (M3) and indirect (M2) contraction; pre-junctional nerve terminals where they increase (M1) or decrease (M4) the release of ACh and noradrenaline (NA/norepinephrine {NE}); sensory nerves where they influence afferent nerve activity; umbrella cells in the urothelium where they stimulate the release of ATP and NO; suburothelial interstitial cells; and finally, other unidentified sites in the urothelium from where prostaglandins and inhibitory/relaxatory factors are released. Thus, the actions of muscarinic receptor agonists and antagonists on the bladder may be very complex even when considering only local muscarinic actions. Clinically, muscarinic antagonists remain the mainstay of treatment for the overactive bladder (**OAB**), while muscarinic **a**gonists have been used to treat hypoactive bladder. The **anta**gonists are effective in treating OAB. Activation of muscarinic ACh receptors in the bladder is thought to induce bladder contractions in humans. ACh directly activate smooth muscles of the bladder by post-synaptic site of action (NT release from nerves). Subjects smoking *cannabis* have reported an improvement in bladder dysfunctions. Currently, the most widely used and effective pharmacologic treatment for OAB is administration of muscarinic receptor antagonists. ACh is the main NT released from the parasympathetic nerves and is responsible for initiating synchronous contraction of the detrusor, resulting in the raised intra-vesical pressure that accompanies micturition (urination). Muscarinic acetylcholine receptors (**mAChR**) mediate a variety of cellular responses, including inhibition of adenylate cyclase [AC], modulation of K+ channels, and increased phosphoinositide [PI] breakdown. These diverse effects of mAChR activation elicit both negative and positive inotropic and chronotropic effects in the heart. Current muscarinic antagonists block mAChRs, producing mydriasis and bronchodilation, increasing heart rate, and inhibiting secretions. Commonly used muscarinic antagonists include **atropine &** **scopolamine**. Administering muscarinic antagonists is a must when the effect of muscle relaxants is antagonized by acetylcholinesterase [**AChE**] inhibitors, causing profound bradycardia, and heart block. In depth studies on CBG showed that its effect of on ACh-induced contractions was not affected by CB1 or CB2 receptor antagonists. Urodynamic studies of anaesthetized animals show the effects of anti-muscarinic drugs such as CBG. Inhibition of the muscarinic receptors leads to a progressive reduction in voiding efficiency, shown by a reduction of peak pressure, and an increase in the frequency of micturition. In mice, **CBG** = THCV>CBD>CBDV (but not CBC) were found to decrease the bladder contractions induced by ACh without any effect on the contractions induced by electrical stimulation. CBG was found to decrease bladder contractions in humans as a result of mAChR antagonism, treating successfully bladder dysfunction.

**Psoriasis treatment:**

As a result of activated keratinocyte killing, CBG was found to heal skin psoriasis. As activated keratinocytes cause this severe skin condition, CBG topical ointment or salve may be affective treatment.

**Glaucoma treatment**:

CBG reduces **i**ntraocular pressure [**IOP**] in eyes of glaucoma patients and eye drops containing CBG are successfully used to treat the disease.

**Combined treatment with CBD + CBG:**

With the recent **de**regulation of CB**D** and Hemp-derived pCBs (The Farm Bill 2018), such as CB**N**, CB**G** & CB**C**; there is a growing interest in **minor pCBs** pharmacology. CBD & CBG are very comparable at 5 receptor potential cation channels (TRPA1, TRPV1,2,3 &4) with minor differences in affinity. CBG is a very potent (sub-nanomolar! affinity) agonist of the alpha-2-adenoceptor whereas, CBD have no such effect. CBG is an **anta**gonist at the 5-HT1A receptor while CBD is an **in**direct **a**gonist of the same serotonin receptor subtype. Physiologic effects of CBG tend towards **Gi** (inhibitory G-protein)-mediated auto-regulatory activity and calcium-based signaling by ion channels and protein kinase C [**PKC**].

CBG, a non-psychoactive molecule, from which all of other pCBs are derived, recently gained momentum as more brands learn of the molecule’s therapeutic benefits in over-the-counter and pharmaceutical application. According to recent investigations, CBG has similar properties to CB**D**, acting as a weak competitive partial agonist for cannabinoid receptors in both the nervous system and immune cells

A 2020 study, that tested PPAR-alpha/gamma agonism by CB**G**, found enhanced differentiation of bone marrow mesenchyme stem cells. This effect was enhanced when **combined with** CB**D**. PPAR-gamma agonists increase the expression of glucose transporter type 4 [**GLUT4**] that increase insulin sensitivity. CBD/CBG combination, improve adipo-genesis (fat accumulation) that improve symptoms of **metabolic syndrome**. CBG can treat both type 2 diabetes and metabolic syndrome (obesity). What CBG does offer is a slew of potential medical benefits without the intoxicating side-effect of THC. For this reason, CBG has been gaining popularity in the cannabis world recently, and will likely be one of the first minor cannabinoids you see featured in dispensary products in years to come. The potential for new revenue streams in the cannabis value chain exists in cannabinoids such as CBG.

Cannabigerol will provide farmers, brands, factories, retailers & dispensaries the ability to deliver better medical solutions in dermatological, gastroenterological [**GI**], athlete's performances - muscle, bone & joint pain relief as well as mental health issues. Despite CBG’s immense benefits, many firms find it difficult to produce, given that it is rarely expressed in common cultivars. It used to take thousands of pounds of biomass to create small amounts of CBGA isolate that’s because most hemp only contains minute percentages [1%] of CBGA. Innovative breeding techniques have recently led to optimized cultivars including those with significantly higher amounts of rare cannabinoids. Companies that have been able to successfully bring to market solutions recently announced an offer of certified feminized seeds with 15% (or even more) CBGA and compliant THC levels [less than 0.3 %].

**Modes of CBG application**

**Oral Tinctures:**

Cannabinoids can enter the blood stream when placed under the tongue and held in the mouth; within the mouth there are a large number of blood vessels which can absorb pCBs. Common examples of these products include dissolvable strips, sublingual sprays, medicated lozenges or oil tinctures. Different formulations of pCBs dissolved in middle chain triglyceride [**MCT**] or Hemp seed oil [**HSO**] is the most popular method among athletes.

**Topical Application - Skin Salve, Ointment & Transdermal Patch:**

One way to consume marijuana is through topical applications. These come in the form of lotions, salves, bath salts and oils that are applied to the skin. The skin has a relatively complex absorption process that is based on a chemical’s ability to dissolve in H20. The cannabinoids penetrate the skin and work to reduce pain and inflammation. This method is very popular with older consumers because it works well on localized pain (like from arthritis) and is non-psychoactive. While not widely studied, there is research that shows that topical application of pCBs has an onset of action within minutes locally (i.e. creams and balms applied to a **joint**), with duration of these effect lasting one to two hours. Individuals who used patches reported onset of action within two hours and duration of effect lasting upwards of two days due to the time released nature of this method of administration. Additionally, the topical application of pCBs does not allow a significant amount of cannabinoids to reach the brain and therefore is unlikely to cause any intoxication.

**Nasal Sprays & Rectal Suppositories** are currently under intensive research & development**.**

***Cannabis* in Sports [HOT NEWS! From the Press]**:

The World Anti-Doping Agency [**WADA**] announced recently it would review the status of *Cannabis* on its prohibited substances list, according to a press release from the agency. While cannabis will remain prohibited in 2022, any changes that stem from the agency's review would not take effect until the following year. This comes after the agency received "requests from a number of stakeholders," the press release said. This move follows the disqualification of 21-year-old **Sha’Carri Richardson**, an American sprinter who became an overnight sensation after winning the women's 100-meter race at the U.S. track and field trials in June 2021. In the days that followed the trials, Richardson received a positive drug test that detected a chemical [THC?] found in marijuana in her system .Though Richardson received a one-month suspension that would have ended before the Tokyo Olympics, her positive drug test negated her qualifying performance at the trials and cut her Olympic dreams short. Richardson's disqualification sparked a larger conversation about the performance enhancing potential of *Cannabis*. The drug is legal in several U.S. states including Oregon, the site of the U.S. track and field trials.

**Affinity [*K*i (nM)] of eCBs & pCBs to CB1 & CB2 receptors**

The **inhibitory constant** (***K*i**) and the IC50 of a drug that is known to cause inhibition of an enzyme or receptor have to do with the concentration needed to reduce the activity by half. More specifically the *K*i is reflective of the **binding affinity** and the IC50 is more reflective of the functional strength of the inhibitor. Since the *K*i takes into account the IC50 in its calculation, the *K*i is being reported more often by pharmaceutical drug companies.

|  |  |  |
| --- | --- | --- |
| **Compound** | CB**1** | CB**2** |
| **AEA** | 78 | 370 |
| **2-AG** | 58 | 145 |
| **THC** | 10 | 24 |
| **CBD** | 1,045/1,690 | 1,714 |
| **CBG** | 440/30,000 | 337/1.225/2,700 |
| **WIN-55,212** | 8 | 3 |
| **JWH-018** | 9 | 3 |

CBG displays *K*i values in the low micromolar[μM] range when competing for the binding to CB**2.** Surprisingly, significant competition in the binding to the CB2R was only observed when using [3H]-CP-55940 (not [3H]-WIN-55,212-2) as radio-ligand. The huge fluctuations in Ki values for CBG is due to different reaction conditions, type of cells & membranes tested and the radio ligand used in the competition experiments, WIN-55,212-2 vs. CP-55,940.

**Final Thoughts: Cannabigerol for Athletes**

Cannabigerol [CBG] is the “mother” cannabinoid of all other phytocannabinoids [pCBs] present in the *Cannabis* plant. Essentially, it’s classified as a minor pCB, but CBG is an extremely important (major) cannabis compound. In the cannabis plant, CBG can be found in the form of cannabigerolic acid (CBGA), which is the building block of the three main branches of cannabinoids that include: cannabidiolic acid (CBDA), tetrahydrocannabinolic acid (THCA), and cannabichromenic acid (CBCA).

CBGA transforms into these three branches of pCBs through specific plant enzymes known as synthases as the *Cannabis* plant matures. Because most CBGA is synthesized into these other molecular structures, there are very low concentrations of CBGA in mature *Cannabis* plants. Through a process of decarboxylation (where heat is applied), CBGA, CBDA, THCA, and CBCA all lose one carbon dioxide group and become **neutra**l pCBs. The acid pCBs are transformed into CBG, CBD, THC and CBC. This is considered the active state of these compounds and where most of their therapeutic benefits are contained.

Not only does CBG show to contain some significant benefits when used alone, but also shows promise when used **synergistically** with other pCBs such as CBD, THC and THCV and several *Cannabis* terpenes.

Cannabinoids apparently act on inflammation through mechanisms different from those of agents such as non-steroidal anti-inflammatory drugs [NSAIDs]. Cannabinoids are generally free from the severe adverse effects associated with NSAIDs. Their clinical development thus provides a new approach to treatment of diseases characterized by acute and chronic inflammation & pain. CBG has shown to contain numerous therapeutic benefits and could play an integral role in the treatment several health disorders and diseases.

CBG is not psychoactive, meaning it is non-euphoric and won’t get you "high". In fact, much like CB**D**, CB**G** could counter some of the negative effects of THC-rich strains, such as paranoia and anxiety. CBG has shown to be a weak partial agonist of CB1 and CB2 receptors which explains why it could mitigate the negative effects of THC. Some of the most significant therapeutic effects of CBG include:

Muscle Relaxant: CBG inhibits gamma amino butyric acid [GABA] **re**uptake that is greater than both CBD and THC, which could suggest muscle relaxant properties that is most important for athletes.

Pain Relief: The analgesic (pain-relieving) properties of CBG are said to surpass those of THC.

Antidepressant: Many studies suggest that CBG contains antidepressant and mood-stabilizing properties. CBG have positive psychological effects, reducing negative emotions (anxiety, depression, fear & anger) while elevating mood & wellbeing. CBG also reduces nausea and increase appetite. Positive vibrations are very important for athletes.

Anti-Cancer: CBG is the second-most effective pCB against breast cancer after CBD. It is also thought to be a potent agent against prostate and colorectal cancer [CRC].

Antifungal & antibacterial: CBG inhibits bacterial fatty acid [FA] metabolism. Research shows that CBG is a powerful agent against fungi and antibiotic-resistance bacteria such as MRSA.

CBG could be beneficial for psoriasis treatment due to its ability to inhibit keratinocyte proliferation.

CBG might help with overactive bladder and bladder pain. Recent study backed up this suggestion by testing the effects of CBG on bladder dysfunction. Results found that CBG and THCV had the greatest capacity for the reduction of bladder contractions.

CBG was found to reduce high blood pressure which is most important for athletes. CBG could **work in synergy** with other *Cannabis* compounds, namely terpenes such as: myrcen, limonene, linalool, phytol, and beta-caryophyllene [BCP], lending to what’s known as the **entourage effect**. Another recent study looked at the neuroprotective properties of CBG in patients with Huntington disease [HD], a condition that causes the progressive breakdown of nerve cells in the brain Symptoms of HD include involuntary movements and muscle problems. The study found that CBG was extremely active as a **neuro-protectant** and helped improve motor deficits in animal models. Another study discovered that CBG (and other pCBs) have the potential to indirectly stimulate **bone growth** by means of the CB**2** receptor activation. CBG hold the potential to heal bone fractures, although further research is certainly needed. A 1990 study looked at the effects of CBG and THC on glaucoma and found that both cannabinoids produced a three-fold increase in aqueous outflow activity, suggesting that CBG may have therapeutic potential in the treatment of glaucoma by lowering the intraocular pressure [**IOP**].

Athletes should not be using prescription pain medications to help with their pain to get through the day. They could have a more natural alternative with no side effects. Our body is already built for cannabinoids, not really for painkillers. That’s why a lot of athletes have issues with their kidneys when they are on painkillers for so long.

Summing-up, CB**G** is a **safe**, **non-euphoric**, **legal,** **natural remedy** for the treatment of sore muscles, joints, ligaments and bones caused by athletic, bodybuilding & endurance sports.

**Tincture Formulations** that contain both CB**D** & CB**G** (and some CB**C**), in the appropriate ratio between the three pCBs, are able to treat successfully muscle, bone, tendon & joint pain and help athletes in their everyday sport activities - both physically and mentally.

Therefore, CBG should be considered as a "minor" pCB

That have **major** therapeutic potential for athletes.