Research Article

To legalize cannabis in Ghana or not to legalize? Reviewing the pharmacological evidence

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Summary

Background: Although illegal, Ghana has a long history of cannabis use. With changing perceptions, advocacy for legalization has increased globally. This study exams pharmacological evidence on the prospects and challenges of decriminalization and /or legalization of cannabis in Ghana.

Results: Cannabis and cannabinoids are a "pharmacological enigma" with unique ability to activate at least 3 of the 4 drug receptor super families. This include; inotropic Transient Receptor Potential Vanilloid 1 (TRPV1), metabotropic Cannabinoid Receptors (CB) and nuclear Peroxisome Proliferator Activator Receptors (PPAR). Cannabinoid receptors also dimerize with other receptors creating distinctly new signaling pathways. Cannabis and cannabinoids show good anti- nociceptive, anti-inflammatory, immunosuppressant anti-emetogenic activity and variable anticonvulsant activity. It can play important role in palliative care, some rare intractable epilepsy, multiple sclerosis, cachexia and Opioid Use Disorder. Cannabis precipitates psychosis in individuals with underlying genetic susceptibility. Chronic cannabis use alter the neurobiology of adolescent brain, predisposing them to amotivational syndrome characterized by depersonalization and inhibited motivation for goal directed behavior. Cannabis is also a "gateway drug"; ushering users to "harder" substances of abuse and reinstating extinguished drug seeking behaviours. The recent tramadol abuse in Ghana may have been precipitated by previous and concurrent cannabis use. Furthermore, Ghana's cannabis may have a higher propensity to induce detrimental effects because of preferential accumulation the psychotropic delta-9-Tetrathydrocannabinol as a result of the high tropical temperature and humidity.

Conclusion: There is not sufficient pharmacological evidence supporting criminalization of medical cannabis in Ghana. However, the same evidence does not support legalization of recreational cannabis.

Introduction

Contemporary media and scientific literature indicate a global surge in interest in the therapeutic effects and recreational uses of cannabis or marijuana [1]. Consequently, perception on cannabis use is rapidly moving towards liberalization with some industrialized countries decriminalizing or legalizing the use [2]. Compared to decriminalization, legalization provides an economic dimension of regulated cannabis cultivation, supply and taxation system. In such jurisdictions, a multimillion dollar cannabis industry is developing, which provides employment and contributes significantly towards Gross Domestic Product. This has led to rechanneling of police efforts to more relevant crimes and has reduced the hold of criminals on the trade [3]. Surprisingly, in some cultures, small scale cannabis business are overwhelmingly against legalization for fear of losing decades old monopoly to large co-operations [4].

Recently, Ghana, a major drug transit hub, has also grappled with the issues of legalizing of cannabis. The Ghanaian state is secular but deeply conservative socially. Substance abuse is underreported due to stigmatization. Nonetheless, some limited data suggest that Ghana's cannabis consumption per capita maybe amongst the top 10% globally. Over 4.5 tonne of cannabis were seized in Ghana in 2017 [5]. Reports on

estimated users range between 8 to 21.5% which is higher than the global average of 3.8% [5,6].

Reasons why cannabis use is popular in Ghana is yet to be determined. Economically, cannabis trade is means of "capital formation" as well as a safety net during cocoa price slump [7,8]. In Ghana, cannabis is relatively cheap compared to other substances of abuse and low cannabis pricing correlates well with abuse [9]. Furthermore, the Ghanaian Boarding Senior High School system is a good breeding group for peer influence to cannabis use. In addition, there is an apparent grey interface between Christianity (the predominant religion in Ghana) and the Rastafarian religion, where cannabis has sacramental uses [2].

This work therefore reviews over five decades of pharmacological research on cannabis and cannabinoids to provide a pharmacological perspective about the prospects and challenges of cannabis use in Ghana.

What is cannabis or marijuana?

Cannabis or marijuana has many local street names including, wee, ganja, ntampi, indian hemp, popo, obonsam tawa ('the devil's tobacco') etc. It may refer to the whole plant or plant part of the dioecious annual flowering plant, *Cannabis sativa or* it closest variety *Cannabis indica of family cannabaceae (*previously *Urticaceae)* or hybrid plant of the varieties [10]. *Cannabis sativa* varieties are taller and have higher phytocannabinoids. Cannabinoids, the main phytochemicals of the plant are in the resins of glandular secretions of the female plant [11]. Typically, dried aerial part is smoked to administer lipophilic phytocannabinoids to the lungs and brain within minutes. Occasionally, cannabis hot infusion (tea), or "Lakka", a popular alcohol extract of cannabis is used although bioavailability of cannabinoids by oral route can be erratic and unpredictable [12].

History about introduction and use of cannabis in Ghana is not clear. There are suggestion that it may have been introduced in early 20th Centuary by returning World War 11 veterans from Indian and Burma. However, the role of Sierra Leonean immigrants and sailors in the propagation and commercialization of cannabis throughout British West African cannot be overemphasized [13]. Not with standing, cannabis has survived and thrived extensively throughout Ghana especially in cocoa growing areas providing income support when global prices slump [8].

Cannabiniods

Classically, the terms cannabinoid, cannabimimetic or cannabinergics are synonymous and describe a diverse group of structurally dissimilar families of compounds that bind to cannabinoid receptors (CB1/CB2) or mimic some of the actions of the major psychoactive substance in *Cannabis sativa*. There are 3 major classes of cannabinoids.

Phytocannabiniods: Over 100 chemically distinct C_{21} terpenophenolics compounds have been identified and isolated from *Cannabis sativa* [14,15]. Gaoni and Mechoulam (1964) first isolated Delta-9-Tetrahydrocannabinol (THC) as the main phytocannabiniod in the plant responsible for its hallucinogenic activity. Other major phytocannabiniods include cannabigerol, cannabichromene, cannabitriol and Cannabidiol. Cannabidiol has been shown to antagonize Delta-9-THC's psychotropic effects [16,17].

The endocannabinoids system: The system comprises receptors, endogenous ligands, enzymes that synthesize and degrade signaling molecules [18].

Two endogenous molecules *N*-Arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) have been labelled as endocannabinoid prototypes. Anandamide ("amide of "delight") is obtained by decarboxylation of phosphatidylserine to phosphatidylethanolamine followed by acetylation [19]. This reaction is carried out by the ubiquitous conjugation enzyme N-acetyl transferase. It is then followed by a series of reactions involving Phospholipase A2, C and D [20]. Similarly, 2-Arachidonoylglycerol (2-AG) is believed to be a degradation product of glycerophospholipids such as inositol phospholipids and several cellular Phospholipase enzymes [21].

Synthetic cannabinoids: These cannabinoids were synthesized to aid in elucidating aspects of the endocannabino-id system. However, they have developed into a distinct pharmacological class use for pharmacotherapy and recreation. The core structure is a bi or tricyclic delta-9-THC compound with a substituted central pyran ring [22]. They possess greater affinity for cannabinoid receptors than delta-9-THC. Popular synthetic cannabiniods such as spice, shatter and K2 have been used as adulterants in herbal preparation and snacks to create mass euphoria and psychosis at public gatherings [22]. Continuous structural modification of the parent molecule has made it a challenge for drug regulatory agencies globally.

Pharmacology of cannabis/cannabinoids

Pharmacology of cannabis and cannabinoids is complex and it is believed to interact with at least 3 of the four major receptor super families which include inotropic Transient Receptor Potential Vanilloid 1 (TRPV1), the metabotropic Cannabinoids receptors (CB), GPCR 55 & 119 as well as the nuclear Peroxisome Proliferator Activator Receptors (PPAR). Molecular techniques have identified two distinct G-protein coupled cannabinoid receptors [23]. The type 1 cannabinoid receptor (CB_1) is predominantly distributed in regions of CNS involved in cognition, memory, reward, nociception, and motor coordination as wells some peripheral visceral tissues. The well-known tetrad of cannabinoids effects i.e, hypoactivity, hypothermia, antinociception and catalepsy occur as a result of CB_1 receptors activation. The type 2

receptor (CB_2) is predominantly found on immune and hematopoietic cells [24]. CB_2 has also been identified in some CNS region and its expression appears to be highly inducible by injury and trauma [25]. Generally, CB receptor activation induces cellular hyperpolarization, decrease cellular cyclic Adenosine Monophosphate levels (cAMP) whilst activating extracellular signal-regulated kinases [26].

However, activations of the classical CB receptors by cannabis does not account for all the myriad of observed pharmacological effects. Cannabinoids bind to Transient Receptor Potential Vanilloid 1 (TRPV1) on small diameter primary afferent fibres leading to reduced sensation to pain. Effects of endocannabinoid on TRPV1 are blocked by capsaicin from chilli but not CB_1 receptor antagonist [27]. Cannabinoids also show strong affinity for binding to Peroxisome Proliferator Activated receptors (PPAR) family of nuclear receptor. These receptors play important role in fat and carbohydrate metabolism, transcription of hepatic enzymes [28]. Moreover, the endocannabinoid prototypes are a biosynthetic product of fatty acid metabolism hence share overlapping physiological effects with products of eicosanoid acid [29].

In addition to activating individual receptors, cannabinoid receptors dimerize with other receptors (either homo or heterodimerization) following concurrent activation creating distinctly new signal transduction pathways. This has been reported cannabinoid CB_1 and dopaminergic D_2 receptors [30].

Medical potential of cannabis and cannabinoids

Analgesia/Antinociception: Cannabis has been used for acute, chronic, inflammatory and neuropathic pain [31]. Infact, antinociception is one of the tetrad of behaviors associated with cannabinoids. CB_1 receptors in the peripheral systems, presynaptic primary afferent C- and Aδ-fiber as well postsynaptic dorsal horn neurons of the spinal cord modulate nociceptive transmission [32]. In addition, CB_1 receptor inhibition of hippocampal neurons calcium channels cause alteration in glutamate release in dorsolateral striatum with arguments anti nociceptive effect [33,34]. Cannabinoids also activate opioidergic pathways in modulating pain [35]. There have been suggestions that a separate metabotropic receptor, GPR55, may be involved in modulating mechanical hyperalgesia. During therapy, cannabinoids synergizes well with other analgesics.

Anti-Inflammatory and immunosuppression: Overwhelming evidence suggests that cannabis is effective in diseases with underlying chronic inflammation and immune cell dysfunction such as asthma, rheumatoid arthritis, Crohn's disease. The immune effects is mediated CB_2 receptors located on immune cells; activation of which alter cellular and humoral immunity [36]. Furthermore, the detection of CB_2 receptors in CNS suggest a possible role of endocannabinoids

in neuro protection and neuro inflammation [37]. This may explain why cannabinoids have been very effective in the management of multiple sclerosis [38]. In *in vitro* studies, cannabis shows bidirectional actions on immune cells i.e, low doses enhance survival and proliferation whilst high doses exert inhibitory effects. Secondly, cannabionoids stimulate the immunologic immune system mediated by T helper Type 2 whilst inhibiting the cellular defense immune responses mediated by T helper Type 1 [24]. This is reflected by changes in their respective cytokines levels [39].

Anti-emetogenic effects: Nausea and vomiting has been a major drawback to cancer chemotherapy. Conventional anti-emetics such as serotonin $5HT_3$ receptors antagonist with corticosteroids have been woefully ineffective at relieving delayed or anticipatory symptoms [40]. A neurokinin NK_1 receptor antagonists was introduced with much greater success. However, neither agents used alone or in combination is effective at suppressing nausea caused by chemotherapy [40].

Cannabis has been employed as anti-emetic, anti-nausea agents over centuries [41]. Cannabis and cannabinoids were putatively accepted as anti-emetic, anti-nausea after patients who actively smoked cannabis showed less susceptible to the emetogenic effect of cancer chemotherapeutic agents. Cannabinoids can protect against 'acute', 'retarded' or 'anticipatory' nausea and vomiting reactions induced by cancer chemotherapy [40,41]. This effect is reversed by CB_1 receptor inhibition implying a possible mediation by CB_1.

Evidence suggest a probable interaction between serotonergic receptors and cannabinoid receptors [42]. More compelling evidence of this interaction is coexpression CB_1 and 5-HT3 receptors in regions involved in vomiting such as the area postrema, nucleus of the solitary tract (NTS) and the dorsal motor nucleus of the vagus. Peripherally, cannabinoids also induce GIT relaxation which attenuates vomiting by enteric serotonergic impulses. This is important as mechanistically, vomiting occurs when serotonin activates $5-HT_3$ on adjacent enteric parasympathetic afferent nerves to activate chemoreceptor trigger zone [42].

Cannabis and cancer: Cannabinoids have been employed in cancer mostly for adjunctive and palliative actions [43]. Epidemiological evidence for an association between cannabis use and decreased incidence of cancer is limited and conflicting [43]. The endocannabinoid system appears to be hyperactive in many cancers and pharmacological manipulation of the receptors usually results in antitumour effects [44]. Cannabinoids show a good degree of selectivity in inducing apoptosis in cancer cells especially in lung, breast, pancreatic, prostate and gliomas [45].

Several apoptotic pathways have been proposed. This include phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), ERK signaling pathways, protein p8, stress-related

transcription factors [44,46]. The anti-tumour activity involve both cannabinoid receptors. The tissue receptor ratio and density may account for variation in response. Consequently, cannabis are procarcinogenic in tissue without cannabinoids receptors or those with low receptor density [47].

Anticonvulsant: There are multiple anecdotal references to the effectiveness of cannabis in epilepsy. However, the first documented clinical evidence on efficacy was by O'Shaughnessy in 1848 [48]. Although delta -9- THC exhibits powerful anticonvulsant activity, there are also clinical evidence showing pro-convulsant activity [49]. Despite these contradictions, virtually all the major phytocannabinoids demonstrate efficacy in maximum electroshock in murine but not all show effectiveness in chemoshock models [50]. Some authors have postulated that cannabinoids are effective at controlling spastic seizure states and some rare intractable epilepsy but are virtually useless in petit and grand mal seizures [49,50]. A survey amongst 215 epileptics who actively use cannabis should that only 7.4% reported that cannabis improved their seizure condition [51]. The scientific evidence supporting the use of cannabis for the treatment of epilepsy is at best weak.

Hyperphagic actions: According to Abel, 1975, the earliest reference to the hyperphagic actions of cannabis was around AD 300. Subsequently, in the last decades cannabis and cannabinoids have been used to promote weight gain in cachexia, HIV wasting and other hyper metabolic states. There are prospects that cannabinoids will may be beneficial in other nutrition related disorders. The mechanism involve enhancement of orosensory acuity of users resulting in preferential overconsumption of sweet foods especially within the first few days of treatment [52,53]. However, animal studies have not been successful at corroborating the human experience and the magnitude and quantum increase in food consumption reported in animal studies were a fraction of the human experience [53].

Concrete scientific evidence implicate CB_1 receptors in brain centers traditionally associated with food such as ventromedial hypothalamus, the nucleustractus solitares [54,55]. This findings is further re-enforced by the ability of CB_1 specific antagonist to reverse hyperphagia [54]. This effect is stereo specificity with only the L- delta-9-THC being effective [56]. Naloxone blocks cannabis induced hyperphagia; suggestion a possible interaction between opioids and cannabinoids [57].

Legalisation of cannabis in Ghana–potential challenges

Neuropsychiatric effects: A major setback to legalization is cannabis neuropsychiatric effects. Cannabis use is high amongst individuals with schizorphrenia, dysthymia and major depression [58,59]. In many instances, the use of cannabinoids precedes the development of neuropsychiatric disorder. Again, cannabis may precipitate acute transient

psychosis in persons with preexisting neurological conditions or those with a positive family history of schizophrenia [60]. In such individuals, adolescent cannabis use can increase the risk of schizophrenia by as much as six folds before the age of 26 [60]. However, as to whether cannabis cause neuropsychiatry disorders is still up for debate as there are no properly controlled population based [59]. Another major setback to this findings is concurrent usage of other illicit drugs by cannabis users. It is however noteworthy that not all people who use cannabis develop acute transient psychosis and schizorphrenia. A complex interplay of environmental (socio-economic and socio-demographic factors) and genetic vulnerability (eg defective Cathecol-O-methyltransferase enzyme) contributes to the development of neuropsychiatric disorder.

Notwithstanding, these epidemiological studies may not predict the effects of cannabis in the Ghanaian context. Although unsubstantiated, Ghana Cannabis has been putatively touted as "High Grade" supposedly due to its high delta-9-THC content. It is known that the high tropical temperature and humidity in Ghana favour the accumulation of psychotropic delta -9-THC over the non-psychogenic cannabidiol (CBD) [61]. At the molecular level cannabidiol antagonizes the psychotropic effects of delta -9-THC [62,63]. The ratio of delta -9-THC/CBD in cannabis inversely correlates to the volume of right hippocampus of the chronic user [64]. Therefore, cannabis with high delta -9-THC/ CBD ration is associated with more schizophrenia-like symptoms [65,66]. All these may suggest that Ghana's cannabis may have a different chemical composition and a possible higher propensity to induce psychosis than that usually used by many researchers.

Cannabis, the reward system and retrograde signaling

According to the dopamine theory of psychosis, excess dopamine in some cortical and mesolimbic centers of the brain causes psychosis [67]. Subsequently, cannabinoids act on CB_1 receptors to activate mesolimbic dopamine system for reward and reinforcing. However, Spiller, et al. [68], postulate that higher dose of cannabinoids attenuate reward and induce aversion by stimulating CB_2 receptors [68]. This may explain the paradoxically effects such as euphoria or dysphoria, anxiolysis or anxiety reported by some cannabis users.

The neurobiological basis for concomitant use of cannabis and other substances of abuse is ability of Delta-9-THC to facilitate the reward of other substances of abuse [69]. The accumulation dopamine in the Nucleus Accumbens, and Ventral Tegmental Area and the rewarding effects of several illicit drugs can be reversed by CB_1 receptor antagonists. These effects were confirmed by the decreased rewarding effects of drugs of abuse by CB_1-null mice [70]. In support of this, CB_1 agonist can reinstate extinguished drug seeking behaviours causing previous drug addicts to relapse [71].

Endocannabinoids acting on CB_1 receptors, modulate proximal neurochemical transmission. This result in retrograde suppression of neurotransmissions to protect against excess presynaptic activity and modulating mesolimbic dopamine releasing. Delta-9-THC disrupts this retrograde signaling of endocannabinoids explaining many neuropharmacological effects of cannabis [72].

Cannabis as a "gateway" to hard drugs

Studies in substance abusers showed a sequential and incremental pattern where cannabis ushers users to addictive "hard" drugs [73]. Many users begin with alcohol or tobacco proceed through cannabis to narcotics, hallucinogens, methamphetamine [74,75]. Fergusson, et al. [76], report a dose dependent relationship between the use of cannabis and use of other illicit drugs. Furthermore, the age of first exposure to cannabis is also a major predisposing factor to the likelihood of the individual using hard drugs. Indeed, it is very possible that the recent abuse of tramadol in Ghana may have been precipitated by previous and concurrent cannabis use. This presupposes that addressing cannabis use in Ghana will putatively address the surge in tramadol abuse. Suffice to say that delaying the use of alcohol and tobacco by adolescents can reduce or delay the use of cannabis and subsequently the use of other hard drugs.

Cannabis induced-apathy

Perhaps, the major drawback to legalizing cannabis is its long-term impact on young and adolescent brains inducing functional and neuroanatomical changes [64,77]. Cannabis use is associated with psychosocial amotivational syndrome characterized by depersonalisation, derealisation and an inhibited motivation for goal directed behavior [78]. There is strong evidence to show that adolescent cannabis abusers exhibit a blunted emotion, apathy, a reduced affect, sense of detachment, difficulty to concentrate on relevant issues, follow routines or successfully master new material [79]. Such adolescents are more likely to exhibit delinquent behaviours, absenteeism, diminished educational achievement and drop out of school [80,81]. Reduced reward sensitivity due to reduced striatal dopamine biosynthesis is largely associated with this cannabis-induced amotivational syndrome [82].

Conclusion

Cannabis has several medical uses and has not shown to be inherently more toxic than several medicines in current clinical practice. There is very minimal pharmacological justification for criminalizing medicinal cannabis use. However, the pharmacological evidence available now is skewed against legalization of cannabis for recreational because its "gateway effects", association with amotivational syndrome, re-ignition of previous extinguished drug seeking behavior and recidivism in former addicts.

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