A review of the current trends on the use of Cannabis sativa for recreational, medicinal applications, and its toxicological health impacts

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Abstract

Aims: Cannabis sativa (Marijuana) finds application in the medical field, recreational drug use, and as a pain reliever notwithstanding increased trends in the death toll associated with marijuana use. Accordingly, this review seeks to explore the emerging trends through which marijuana is consumed, and the chemicals produced in the course of its use which may trigger medical and toxicological effects. Methods: Relevant articles were identified from database search published during the period 2012 – 2020 in PubMed, Crossref, Google scholar and Web science. The articles were considered if they addressed marijuana use, impacts to users and non-users, carcinogenicity, medicinal value and Covid-19 management by impeding serine protease TMPRSS2 that the corona virus require to penetrate the human host cells. A number of methods by which marijuana is used have been identified with each method producing different results among users. Results: Cannabis sativa has found medicinal value in the management of cancer and human immunodeficiency virus (HIV/ AIDS) patients to alleviate pain and improve appetite, respectively. Even though marijuana is prohibited, there is limited documentation in literature that extensively reports on its toxicological mechanisms. On the contrary, scientific studies emphasize its use in medical applications including its possibility as a cure for SARS-Cov-19 pandemic. Conclusion: Campaigns to legalize cannabis for use in clinical medicine are fundamentally recommended despite its possible toxicological impacts and psychotic related problems. The application of Cannabis sativa in medicine especially in the management of corona virus disease 2019 (Covid-19) and perceived harm is important in research.

1 Introduction

Marijuana is the second most widely and illegally abused drug substance smoked across the globe after tobacco, mainly due to the psychoactive effects ingredient induced by Δ-9-tetrahydrocannabinol ([?]-9-THC) indicated as **1** in Fig. 1, obtained from dried leave stems, seeds and flowers of the *cannabis sativa* hemp plant.[1] The complexity of cannabis plant is defined by the presence of various compounds that induce psychoactive effects on individuals who consume it. Currently, over 500 chemical compounds have been identified in marijuana with over 60 cannabinoids which generate more than 2000 compounds in marijuana smoke through a series of pyrolysis reactions.[1, 2] With an exception of the main psychoactive alkaloid in cannabis, other cannabinoids such as cannabidiol (CBD) delta-8-tetracannabinol (d-8-THC) and cannabinol, designated as **2, 3** and **4** in Fig. 1, contribute to its pharmacological effects[3]. THC introduction to users biosystem induces a number of effects characterized by the alterations in memory, movement, mood, perception and cognition, and in some cases increased dopamine release that ultimately produce euphoric sensations and anxiolytic effects.[4] CBD forms almost 40% of the cannabis extracts from the *Cannabis sativa* plant and is

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mainly found in seeds, stalks and flowers of marijuana offering antipsychotic and alerting properties when consumed, and this forms the basis for pharmaco-therapies[5].
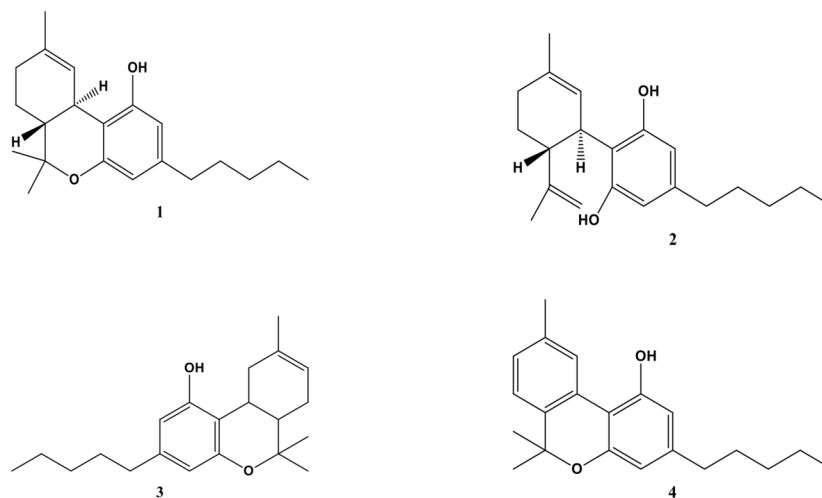

Fig 1 Marijuana cannabinoids

When marijuana is smoked, these compounds find their way into the smokers' body system where they cause a series of disruptive effects among various organs including the pulmonary, respiratory and the central nervous systems.[1] Even though there are minimal reported mortality cases arising from marijuana use among consumers, its increased illegal trading in black markets and consumption patterns precipitate concerns on its potential hazardous effects on human health especially because they are precursors for cancer development, and efforts made towards its abuse cessation has been made by a push to legalize its use, basically for medicinal concerns. Nonetheless, marijuana smoking has been recognized as a risk factor for a pulmonary function and respiratory complications by a number of systematic and epidemiological studies.[6] The motivation behind this review is to examine the apparent harm and psychotic impacts arising from repeated use of this psychoactive drug substance and the scientific efforts advanced towards its cessation from a review of selected published articles from different journals and databases. The emerging chemicals from cannabis cigarette smoke and their cancer potency is the primary focus of this work. On the other hand, scientific efforts taken in order to reduce marijuana toxicity have also been evaluated. Moreover, marijuana legalization for medicinal purposes as anti-inflammatory, antioxidant, neuroprotective and anti-convulsant characteristics has grown in a number of states and nations in the world upon the assumption that it contains chemical compounds that have potency toward treating a number of illness and symptoms regardless of associated risks.[7] Therefore, the application of marijuana as a pharmaceutical drug has also been reviewed in this study especially its use in the management of the severe acute respiratory syndrome corona virus-2 (SARs-Cov-2).[8, 9] These research findings may direct further research in promoting methods that can enhance cessation and control marijuana use and thereby promoting a healthy livelihood of the human race. The literature considered for this study is only published in English language. After the search on the multidisciplinary databases and google scholar, a number of published reports on the subjects of interest especially on marijuana smoking, toxicity and carcinogenicity were the main search terms.

From the surveyed literature, it can be predicted that in the pharmaceutical industry, cannabis is a potential drug agent in pain relieving medications that are required by cancer patients under chemotherapy, neurological issues and even HIV and AIDS patients to aid in appetite restoration. In line with these characteristics, cannabis is likely to offer more benefits in the medical field if clear handling rules and control measures are

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outlined by more countries across the world to provide room for extensive scientific research based on its medical benefits.

2. Methodology

Literature search was comprehensively conducted in search engines such as PubMed, Google scholar and online scientific electronic library from March 2020 to May 2020 in accordance with procedures formerly described by.[10] The search was independent and solely done by selecting databases that included original articles published in peer-reviewed journals, books, thesis, dissertations, patents and other reports that covered *Cannabis sativa* dated until May 2020. Articles published between 2012 and May 2020 was considered if it had information regarding marijuana toxicity and medicinal properties. Further searches were conducted in google search engine by including general terms such as; marijuana toxicity, cancer, carcinogenicity, dangers, intake methods, throat cancer, smoking, cigarettes and cessation. Where there was need, the search outputs were saved in databases and the authors received notifications for searches that met the search criteria from science direct, PubMed, crossref and google scholar. The Marijuana plant - *Cannabis sativa* (Marijuana) is a flowering plant belonging to the family Cannabaceae, although the number of species within the genus is still debatable. Fig 2a presents Marijuana leaves, whereas Fig 2b presents the plant Marijuana, respectively.

Fig 2 (a) Marijuana leaves and (b) Marijuana plant

3. Results and discussion

3.1 Emerging trends in marijuana intake techniques

The effects induced on users by cannabis once consumed are largely dependent on the method of delivery. There exist three major cannabis delivery techniques including inhalation, oral and topical, that has been frequently applied in different occasions with each method having various designed techniques that offer unique functions and results.[11] Smoking and vaporization are the most prevalent ancient customary inhalation methods that are commonly used and involves the use of hand pipes, water pipes, paper rolls (joints/ blunts), hooker and shisha (Table 1).[12] On the other hand, vaporization technique encompass the usage of vaporizers that steadily heat up cannabis herbs to temperatures high enough to extract THC, CBD and other cannabinoids but too low to expedite the release of harmful toxins such as benzene and toluene as well as odor, which are emitted thereby presumably, lowering the associated health risks throughout marijuana smoking duration.[13] This technique is widely used and differs from traditional smoking given that it does not involve combustion. For this reason therefore, vaporization method is considered safer in that it minimizes exposure to the potentially harmful marijuana smoke effluents that could be carcinogenic and toxic to the

health of both active and passive smokers. A range to marijuana ingestion methods and their popularity is reported in Table 1.

Table 1 : Marijuana consumption techniques and popularity trends

Method of intake	Designed Techniques
smoking	**Blunt**: cannabis rolled into a cigar removed of tobacco
	Joint: cannabis rolled in paper and smoked
	Pipe: cannabis smoked in a glass pipe
ingestion	drinks
ingestion	food
ingestion	lozenges
vaporizing techniques	**Bong**: burned cannabis bubbled through water
	Hookah: cannabis mixed with flavored tobacco and smoke bubbled through water
	Dabbing: cannabis products chemically dissolved in solvent vapors
	G-pen: Cannabis concentrated into wax, oil, or hash and vaporized through e-cigare
skin and mucosal surface absorption	creams
	patches
	sprays

Vaporized cannabis includes the use of vape pens, dab rigs and desktop vaporizers like volcano medic vaporizer. In comparison, vaporized and smoked THC have similar pharmacokinetics profiles but on contrary, vaporizers produce higher THC concentrations compared to smoked cannabis resulting to greater THC concentrations in blood, drug effect, mouth dryness and dry irritated eyes when same doses are smoked and vaped.[16] Oral methods include techniques that administer cannabis through the mouth such as edibles and tinctures. For instance, edible are drinks, foods and lozenges which have been infused with THC while tinctures include liquid cannabis extracts consumed by placing 3-4 drops under the tongue and gets immediately absorbed into the body.[15] Consequently, marijuana products are classified as liquids (butane, hash oil, distillate), soft solids (wax, budder), and hard solids (shatter, crumble).

3.2 Emerging chemicals from marijuana and their cancer potency

A good number of scientific research have extensively identified the chemical composition of marijuana smoke and evidently showed that there exists a close similarity in chemical composition between second hand marijuana and tobacco smoke with major differences being component concentrations variations with remarkably similar chemicals including but not limited to nitric oxides and aldehydes which have been proven to cause detrimental health effects.[18] A variety of toxic molecular compounds isolated from marijuana and their classification are presented in Table 2.

Table 2 Some carcinogenic chemical compounds reported present in marijuana

Chemical compounds	carcinogenicity	Ref.
carbon monoxide	Not listed	[19]
benzene	Group 1	[19]
formaldehyde	Group 1	[20]
polycyclic aromatic hydrocarbons (PAHs)	Group 1, Group 2A and group 2B	[21]
hydrogen cyanide	Not listed	[19]
benzo(a)pyrene (BaP)	Group 1	[22]
heterocyclic aromatic amines	Not listed	[23]
aldehydes	Group 1	[24]

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Chemical compounds	carcinogenicity	Ref.
phenolic compounds	Not listed	[19]
volatile hydrocarbons,	Group 2A	[19]
toluene	Group 3	[19]
furan	Group 2B	[19]
2-methylfuvan	Not listed	[19]
isobutylene	Group 1A	[25]
ter-penes and terpenoids	Group 2B	[26]
tetrahydrocannabinol	Not listed	[27]
cannabidiol	Group 2B	[28]

There is substantially less scientific research that has explored the chemical characterization of marijuana cigarette smoke and most studies have focused on determining cannabinoids in marijuana smoke and reported it to contain most of the same toxins, irritants and carcinogens commonly present in tobacco smoke.[29] For instance, when smoked, marijuana produces more tar with more concentrations of carcinogens such as benzo[a]pyrene as compared to tobacco smoke, and consequently it has been classified as a secondary carcinogen possessing 50% to 70% more carcinogenic polycyclic aromatic hydrocarbons such as benzo[a]anthracene, benzene and phenols in greater amounts alongside toxic gases and reactive oxygen species 20 times higher than in tobacco.[30] Notably, these variations in carcinogenic compound concentration in marijuana increase its probability of causing lung cancer in the same way tobacco does, and which has been credited as the leading cause of lung cancer.[29] Nevertheless, it can be presumed that smoking of marijuana is a precursor for respiratory disease and cancer similar to those caused by tobacco smoking, but on the other hand, there is minimal literature reporting or demonstrating that marijuana smoking causes cancer.[31] Furthermore, it has been suggested that marijuana smoke comprises of particulate matter that is harmful and carcinogenic when inhaled because it contains potent compounds such as volatile organics and aromatic amines.[29]

3.3 Harms and health impacts arising from consumption of cannabis

Smokers are driven to smoke marijuana due to its induced psychotropic effects characterized by pleasurable feeling, euphoria and relaxation with psychotic symptoms, cognitive changes, panic reactions and anxiety having been reported as the severe side effects.[32]Epidemiological evidence has linked lung disease, increased respiratory and cardiovascular symptoms, chronic bronchitis and chronic obstructive disease and emphysema to marijuana smoking.[33] In some instances, marijuana use causes alterations and sometimes loss in memory characterized by slowed reaction time, hampered information processing, un-coordinated motor perceptions and performance, and attention deficiency that result in mood syndrome, psychosis and schizophrenia.[34] Accordingly, a review on the effects of marijuana smoking on the lungs found out that prolonged cannabis smoking leads to lung cancer and cancers of the upper aero digestive tract[35]. Moreover, a brief exposure to second hand marijuana smoke leads to acute vascular endothelial dysfunction[36]. Nonetheless, luck of sane mental control due to the detrimental effects of cannabis in intoxicated drivers has been reported to increase the risks of road accidents.[37]The occurrence of these events is hypothesized by the fact that when one smokes marijuana joint he/she is four times exposed to carbon monoxide and five times more tar deposition than a single tobacco cigarette, due to more deep inhalation and longer holding breath times and luck of cannabis cigarette filters.[33] Consequently, psychiatric disorders in marijuana smokers have been associated with acute and chronic smoking.[38] As a result, young cannabis users are likely to experience a deficiency in mental performance by displaying slowness in information processing, amnesia and deprived attention which adversely affects their learning faculties.[34] In addition, pregnant women who get exposed to cannabis are more likely to experience weakened visualization and dexterity and give birth to children that are prone to abnormal behaviour in their late developmental stages.[1]

Once the presence of cannabis is detected in the human central nervous system (CNS), it excites the production of dopamine and endogenous opioids with inhibition of the secretions of acetylcholine that result to

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pharmacological changes in the brain and a consequential decrease of glutamatergic synaptic transmission which causes brain functioning abnormalities among cannabis smoking community.[39] The endocannabinoid system receptors, CB1 and CB2 offer inhibitory function, where CB1 receptor act on the production of cyclic adenosine monophosphate pathway once they receive a signal by adenyl cyclase inhibitor activation while CB2 receptor plays a role in blocking inflammatory activity and tissue damage.[1] Therefore, brain structural abnormality has been observed in chronic cannabis smokers with more effects imposed on the grey and white matter density.[34] Further, variable brain activity in cannabis consumers has been reported compared to non-smokers in which greater brain activation is observed in the prefrontal region of smokers while hypo-activation is noted along the left superior parietal cortex due to high concentrations of the two cannabinoids THC and CBD, THC alters the hippocampal capacity and neurochemistry while on the other hand, CBD defends against toxic variations.[40]

Nonetheless, cerebral stroke, one of the leading causes of death has been associated with cannabis intake according to a number of preclinical studies and scientific case reports.[41]Scientifically, neurological stroke and Alzheimer's disease solely result from exposure to reactive oxygen species such as peroxynitrite, hydrogen peroxide, epoxides etc. and oxidative stress pathways that cause tissue and cellular damage which is largely promoted by cannabis smoking.[1] Accordingly, THC is a potential agent of oxidative stress and a threat factor in the initiation of ischemic stroke.[42] Reactive oxidative stress compounds can be generated by combustion reactions that occur during marijuana smoking.

## 3.4 Application of cannabis as medicine for the management of Covid-19

Pharmacological and toxicological properties of cannabis are contributed by eighteen classes of chemicals which include hydrocarbons, sugars, simple fatty acids, terpenes, amino acids, and nitrogenous compounds.[43] Accordingly, cannabis has been reported to find its application in medicine in treating oncology patients[44], epileptic patients[45], management of inflammatory bowel disease[46], neurological and psychiatric disorders[34] and sometimes in children to treat autism spectrum disorder, fetal alcohol spectrum disorder and in pregnant mothers in the management of hyperemis gravidarum.[7] This has been attributed to the non-psychoactive cannabinoid CBD which interacts with the CB2 receptor that gets activated to reduce pain, seizures and inflammations in patients and sometimes in the management of epilepsy, schizophrenia and post-traumatic stress disorders.[1] Evidently, therapeutic capacity of THC against chronic pain and sclerosis neurological ailments has also been reported.[34] Some studies have reported the application of marijuana in in the treatment of HIV patients to improve their food intake by helping in their appetite and increasing ghrelin and leptin hormones, and decreasing peptide tyrosine hormone responsible for appetite regulation.[47]

In addition, the application of medicinal marijuana in management of corona virus disease 2019 (Covid-19) has been explored by a couple of scientific studies. Covid-19 is and infectious disease that occurs as a result of the SARS-CoV-2 in humans[48], which has not found any medical cure by the time this review, was done. Therefore in the search for a vaccination or cure, the application of Marijuana has been explored by scientists who have given preliminary findings showing that the plant may offer resistance to SARS-CoV-2.[8]The principle behind this is based on the fact that medicinal cannabis has been used to treat nausea and dementia, therefore offering hopes that the angiotensin converting enzyme II (ACE-2) receptor needed by the corona virus found in the lung tissues, oral and nasal mucus, and gastrointestinal tracts can be modulated using cannabis extracts and removed from these parts in order to inhibit vulnerability to the virus and thereof reduce infection risk.[49] Furthermore, terpenes from cannabis have exhibited potent characteristics as antiviral agents with the ability to minimize severity and impact of SARS virus by suppressing the protein responsible for RNA replication and thereby blocking the virus from penetrating the cells.[8] For instance, it has been emphasized that marijuana extracts can reduce or regulate serine protease TMPRSS2 mainly required by the SARS-Cov-2 in order for the virus to gain entry into the human host cells.[8, 9] Consequently, cannabis has been reported to be effective in preventing and treating Covid-19 even though there is limited scientific studies that have been performed to support or refute these assertions especially the role played by cannabinoids towards viral therapy.[50]

3.5 Pharmacokinetics of cannabis

Cannabis just like any other drug substance once taken into the body system describes a systematic pathway from the time it gains entry into the body system up to the time it is excreted after series of biological activities that involve absorption, distribution, metabolism and excretion, all which are dependent on the drug bioavailability that determines the onset, duration and the intensity of effects manifested by the drug.[51] Cannabidiol has been put into use under uncontrolled terms to offer therapeutic effects in many occasions thus raising concern on its therapeutic drug monitoring. According to Millar et al (2018), CBD has found a widespread therapeutic application but still there exists lack of data and discrepancies in its pharmacokinetics.[52] The route of administration of cannabis into the human body system determines the rate by which it is absorbed and its metabolism due to variations in consumed drug concentration.[53] Precisely, when tetrahydrocannabinol (THC) is inhaled and assimilates through the pulmonary system, the associated psychotropic effects are manifested within a period of less than 1 minute but reach a maximum after 20 to 30 minutes, but when it is ingested orally, it takes about 30 to 90 minutes for the psychotropic effects to occur approximately reaching a maximum after 2 hours and remain activated in the smoker for 4 to 12 hours depending on the dose smoked.[11, 53, 54] Cannabis inhalation is characterized by puff numbers, residence time and interval as well as inhalation volume and hold times which greatly influence its bioavailability.[54] In general, cannabis pharmacokinetics is dependent on smoker related factors in addition to chemical properties of cannabinoids and other compounds present in the smoke.[43] Accordingly, smoker related factors embracing age, genetic makeup, renal function and sex which vary from different smoking population across the world, greatly determine the extent to which marijuana pharmacokinetic profiles are expressed.[51]

Metabolic activities on THC take place particularly in the liver where microsomal hydroxylation and oxidation processes occur.[43] Hydroxylation step involves the conversion of THC into 11-hydroxy-THC under cytochrome P-450 complex enzyme catalysis and subsequently, 11-hydroxy-THC oxidized to 11-nor-9-carboxy-THC which glucuronates to THC-COOH beta glucuronide that lacks psychotropic properties [43, 55] as illustrated in Scheme 1, before being excreted though kidneys, faecal matter and urine.[52]

delta-9-tetrahydrocannabinol

11-OH-THC

glucuronide

11-nor-9-carboxy-THC
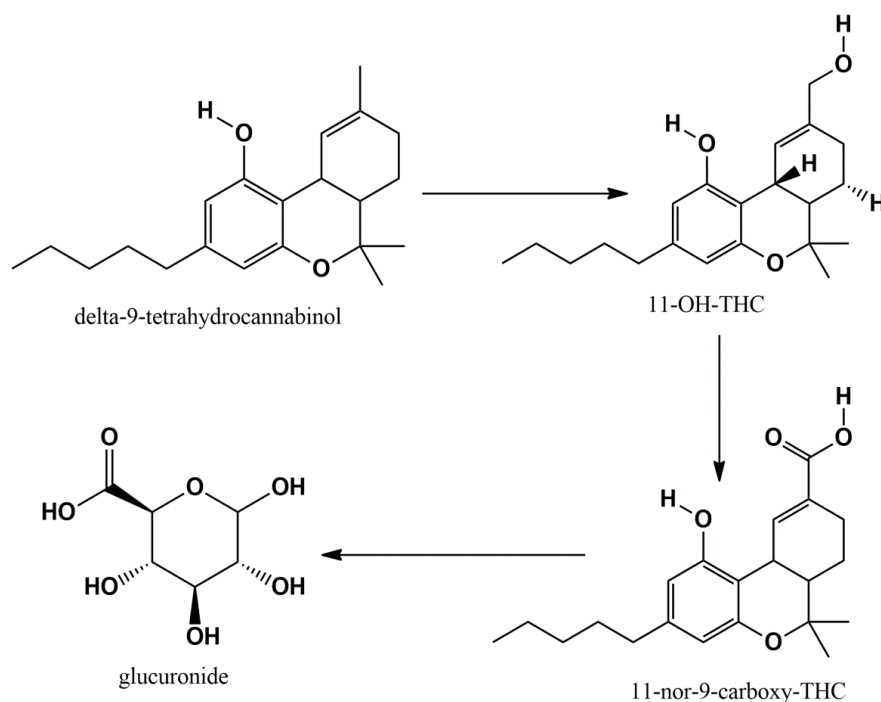
Scheme 1 : hydroxylation and oxidation of THC metabolic route

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On the other hand, CBD gets metabolized by isozymes CYP2C19 and CYP3A4 through hydroxylation to 7-hydroxy cannabidiol (7-OH-CBD) which is further metabolized and ultimately excreted through faecal and urine.[56]

During removal process, the half-life elimination period for THC and CBD vary depending on how long it takes for equilibrium to be attained between blood and lipid storage compartment duration.[54] Accordingly, heavy cannabis users exhibit a fairly longer THC elimination half-life of about 22 hours because of slowed redistribution rates from deeper fatty acid compartment tissues.[54, 57] Similarly, CBD has long elimination half-life of about 34 hours once inhaled.[58]

4. Conclusion

This review has demonstrated that Cannabis is one of the highly consumed prohibited drug substance although it has been legalized in some countries such as Canada for recreational and medicinal use due to cannabinoids present in it. Arguably, there is a rise in the rates of cannabis consumption across the world and with various designed techniques that enable the consumption of this drug. Some of the identified techniques include smoking, vaporizing techniques, skin and mucosal surface absorption with each method offering exceptional and dissimilar outcomes. Nonetheless, this drug is in many ways considered dangerous for human consumption but there is limited number of research that has expressively reported the perceived cannabis toxicity and its cancer precursor characteristics. Although various authors have linked cannabis to human throat cancer and cancer of the respiratory tract system, there is luck of substantive evidence that establishes the mechanisms by which cannabis and its cannabinoids induces cancer. Instead, other toxic compounds produced during cannabis smoking such as carcinogenic polycyclic aromatic hydrocarbons like benzanthracene, benzene and phenols, toxic gases and reactive oxygen species have been identified to be present in cannabis smoke and therefore likely to initiate cell mutations among smokers which eventually initiate cancer. On the contrary, cannabis has found application in the medical field in the management of cancer patients to relieve pain, inflammatory bowel disease, epilepsy, neurological problems and psychiatric disorders. Besides, cannabis has been identified as a potential lead in finding the cure for treating Covid-19 diseases because of its high potency as antiviral agent even though more scientific studies and clinical trials are necessary.

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