Cannabis use and its impact on respiratory physiology and lung cancer risk: Mechanistic and epidemiological insights (Review)

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Abstract. Cannabis use has become increasingly prevalent due to legalization and social acceptance, raising concerns about its potential health impacts, particularly on respiratory and oncological outcomes. Despite sharing toxic constituents with tobacco smoke, including polycyclic aromatic hydrocarbons and volatile organic compounds, the link between cannabis smoking and lung cancer remains inconclusive. Epidemiological studies present conflicting findings, with some suggesting increased risk among heavy users, particularly when combined with tobacco, while others find no significant association. Chronic cannabis smoking has been associated with respiratory symptoms such as cough, sputum production and wheezing, often resembling chronic bronchitis. These symptoms may resolve upon cessation, indicating inflammatory rather than structural damage. Unlike tobacco, cannabis smoking does not consistently induce emphysema but may cause airflow obstruction and increased lung volumes with heavy and prolonged use. Additionally, cannabis smoking impairs alveolar macrophage function, diminishing antimicrobial capabilities and potentially increasing susceptibility to respiratory infections. While cannabinoids such as Δ^9-tetrahydrocannabinol and cannabidiol exhibit potential antineoplastic effects in experimental models, chronic inhalation of cannabis smoke may negate these benefits through exposure to carcinogenic byproducts and chronic inflammation. The concurrent use of tobacco and cannabis amplifies respiratory risks, suggesting a synergistic effect. Given the rise in cannabis consumption and potency trends, ongoing research is essential to clarify long-term respiratory and oncological impacts. Public health strategies should focus on harm reduction and promoting non-combustible methods of cannabis use, while healthcare providers should educate users about the potential risks associated with chronic smoking. Further longitudinal studies with standardized exposure metrics are necessary to resolve existing uncertainties and inform safer use practices.

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Abbreviations: AMs, alveolar macrophages; BAL, bronchoalveolar lavage; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; CBD, cannabidiol; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CUD, cannabis use disorder; ECS, endocannabinoid system; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio; HRCT, high-resolution computed tomography; MR, mendelian randomization; NO, nitric oxide; OR, odds ratio; PAHs, polycyclic aromatic hydrocarbons; RR, relative risk; THC, tetrahydrocannabinol; VOCs, volatile organic compounds

Key words: cannabis, lung cancer, respiratory health, physiology, CBD

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1. Introduction

Lung cancer remains a leading cause of cancer-related morbidity and mortality worldwide, with an estimated 1.8 million deaths annually (1,2). Tobacco smoking is unequivocally recognized

as the primary risk factor, accounting for ~85% of lung cancer cases (3,4). However, as cannabis use becomes increasingly widespread due to legalization and social acceptance, concerns have arisen regarding its potential role in respiratory pathology and carcinogenesis (5).

Cannabis smoke shares numerous toxic and carcinogenic compounds with tobacco smoke, including polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs) and reactive oxygen species (6). These substances have been implicated in DNA damage, oxidative stress and chronic inflammation, all of which are critical pathways in lung carcinogenesis (7). Nevertheless, epidemiological evidence linking cannabis use to lung cancer remains inconclusive and is complicated by factors such as concurrent tobacco use, variability in cannabis potency, and differences in smoking patterns (8,9).

One of the unique aspects of cannabis smoke is its bronchodilatory effect, mediated by Δ^9-tetrahydrocannabinol (THC) interacting with cannabinoid receptors in the bronchial smooth muscle (10). This bronchodilation may transiently counteract airflow obstruction, contrasting with the airway constriction commonly induced by tobacco smoke (11). However, chronic cannabis use has been associated with increased respiratory symptoms, including cough, sputum production and wheezing, akin to chronic bronchitis (12). It has been suggested that while cannabis smoking may impair large airway function, it does not typically cause emphysema or severe airflow limitation as tobacco smoking does (13).

The paradoxical nature of cannabis and its health impacts is further compounded by its pharmacological profile. In addition to its harmful constituents, cannabis contains cannabinoids, such as cannabidiol (CBD) and THC, which have demonstrated anti-inflammatory, bronchodilatory, and even antineoplastic properties in preclinical models (14,15). These conflicting biological effects make it challenging to ascertain the net impact of cannabis smoking on lung cancer risk.

Given the increasing prevalence of cannabis use, particularly among younger adults and populations with chronic medical conditions, there is an urgent need to elucidate its long-term effects on lung health and cancer development. The present review aims to critically assess the current evidence regarding cannabis smoking and its implications for lung cancer and respiratory physiology. By examining both epidemiological data and mechanistic insights, it is sought to provide a balanced perspective on the potential respiratory risks associated with cannabis use, while highlighting the gaps that warrant further research.

2. Overview of cannabis

Cannabis, a plant with a rich history of use in both medical and recreational contexts, has long been a subject of scientific inquiry due to its complex effects on the human body. The plant contains various chemical compounds known as cannabinoids, the most studied being THC and CBD, which interact with the body's endocannabinoid system (ECS). ECS plays a key role in regulating various physiological processes, including mood, appetite, pain sensation and immune responses (16).

General overview of cannabis. Cannabis has been used for thousands of years, originating in Central Asia and spreading across various cultures for medicinal, recreational and industrial purposes. Its therapeutic potential was recognized early on, with significant interest in its analgesic, anti-inflammatory and antiemetic properties (17).

Despite historical stigma, cannabis has gradually gained acceptance, particularly in modern times with the advent of medical marijuana programs in various countries (18).

The psychoactive properties of cannabis are primarily attributed to THC, which binds to cannabinoid receptors 1 (CB1) in the brain, producing a variety of effects, including altered perceptions, euphoria, and, in some cases, anxiety or paranoia. CBD, on the other hand, is non-psychoactive and has gained attention for its potential to mitigate the effects of THC, offering anxiolytic, anti-inflammatory and neuroprotective benefits (19).

Modern use and legalization trends. In recent years, the landscape of cannabis consumption has evolved markedly. With the ongoing legalization of cannabis for medical and recreational use, particularly in regions such as North America and parts of Europe, cannabis has become more widely available. This has led to changes in public attitudes and increased usage, with a corresponding rise in demand for various cannabis products, ranging from traditional dried flowers to oils, edibles and vaping products (20).

Surveys show that cannabis use is rising across various demographic groups, particularly in regions where legalization has occurred. Legalization has also resulted in more robust research on cannabis's effects, and as regulations evolve, new cannabinoid-based therapies are emerging, leading to further interest in its medical applications (21).

Health and safety considerations. The increasing popularity of cannabis, particularly among younger adults, older populations, and individuals with chronic conditions, underscores the importance of studying its long-term health effects (22). While cannabis is generally considered to be safe when used in moderation, there are concerns about its psychological and physical effects, particularly when used heavily or at a young age. Long-term use has been linked to cannabis use disorder (CUD), mental health disorders, and potential risks associated with smoking, such as respiratory problems (23).

It is crucial to understand the impact of cannabis potency, as recent trends show an increase in the concentration of THC, which may exacerbate these risks. While cannabis is often observed as a safer alternative to other substances, such as alcohol or opioids, further research is needed to fully understand its health implications, especially as it becomes increasingly integrated into both medical treatments and recreational use.

Potential medical benefits and risks. Cannabis's therapeutic potential is being explored in a variety of clinical settings. It is increasingly prescribed for a wide range of conditions, including chronic pain, anxiety, epilepsy, nausea and vomiting associated with chemotherapy, and neurological disorders such as multiple sclerosis. However, the balance between benefit and risk is complex, and much of the clinical evidence is still emerging (24).

While cannabinoids show promise in treating various conditions, there is a need for rigorous clinical trials to establish clear dosing guidelines, safety profiles and long-term effects. In particular, research is needed to evaluate the benefits and risks associated with different consumption methods, such as smoking, vaping and edibles (25).

Cannabis and its derivatives have been studied for a wide range of medical indications. Robust evidence supports its efficacy in the management of chronic pain, particularly neuropathic pain, where cannabinoids can provide modest but clinically meaningful benefit (25). Cannabinoid preparations also reduce chemotherapy-induced nausea and vomiting and may improve appetite in patients with human immunodeficiency virus/acquired immunodeficiency syndrome or cancer-related cachexia (26,27). Nabiximols, an oromucosal spray containing THC and CBD, has shown effectiveness in reducing spasticity in multiple sclerosis (28). There is emerging evidence for potential roles in anxiety, post-traumatic stress disorder and sleep disorders, though findings remain inconsistent and often limited by small sample size (29,30).

Conversely, risks of cannabis use are substantial and dose-dependent. Acute adverse effects include impaired short-term memory, psychomotor performance deficits and increased risk of accidents (5). Regular heavy use has been associated with cognitive impairment, development of CUD, and increased risk of psychosis in genetically or clinically vulnerable individuals (31). Pulmonary risks, particularly from smoked cannabis, include chronic bronchitis and airway inflammation (32), while cardiovascular concerns such as arrhythmia, myocardial infarction and stroke have been reported, especially among young adults with underlying risk factors (33,34). Additionally, prenatal cannabis exposure has been linked to lower birth weight and potential neurodevelopmental effects in offspring, though data remain mixed (35).

Chemical structures of common phytocannabinoids, endocannabinoids and synthetic cannabinoids. Phytocannabinoids, endocannabinoids and synthetic cannabinoids share structural similarities while exhibiting distinct chemical compositions that influence their pharmacological effects. Phytocannabinoids are natural compounds produced by the *Cannabis sativa* plant, with the most studied representatives being Δ9-THC, CBD, cannabigerol (CBG), and cannabinol (CBN). Δ9-THC, the primary psychoactive compound in cannabis, features a dibenzopyran ring structure with a pentyl side chain. CBD, a non-psychoactive counterpart, shares a similar ring structure but possesses a hydroxyl group at the C1 position. CBG serves as a precursor to both THC and CBD and is characterized by its linear structure and pentyl side chain. CBN, an oxidative degradation product of THC, retains a similar ring structure but lacks the double bond at C9 (36). These phytocannabinoids differ in their affinities for cannabinoid receptors (CB1 and CB2) and can interact with additional receptor systems such as transient receptor potential (TRP) channels and peroxisome proliferator-activated receptors (PPARs) (37).

Endocannabinoids are endogenous compounds produced within the human body that bind to cannabinoid receptors and are synthesized on demand rather than stored. The primary endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Anandamide, an ethanolamide linked to arachidonic acid, acts as a partial agonist at CB1 receptors and has limited efficacy at CB2 receptors. By contrast, 2-AG, an ester of arachidonic acid and glycerol, serves as a full agonist at both CB1 and CB2 receptors (27). Virodhamine, another endocannabinoid, functions as a partial agonist at CB1 and an antagonist at CB2, highlighting the complex signaling nature of endogenous cannabinoids. Unlike classical neurotransmitters, endocannabinoids are rapidly synthesized and released upon cellular demand, followed by rapid degradation via enzymes such as fatty acid amide hydrolase and monoacylglycerol lipase (37).

Synthetic cannabinoids (SCs) are laboratory-created substances that mimic the effects of THC but are often significantly more potent and toxic. These compounds are structurally diverse, typically featuring an indole or indazole core linked to a carbon tail, which enhances receptor binding affinity and efficacy compared with natural cannabinoids (38). Examples include JWH-018 and JWH-073, which are amino-alkyl-indole derivatives that act as full agonists at CB1 receptors, and AB-FUBINACA, an indazole-based synthetic cannabinoid with high CB1 affinity. Additionally, CP 47,497 and HU-210 are synthetic cannabinoids known for their potent CB1 agonist activity (39). Synthetic cannabinoids exhibit higher receptor affinity and are often associated with severe toxicological effects due to their full agonist behavior at cannabinoid receptors (38).

The structural differences among phytocannabinoids, endocannabinoids and synthetic cannabinoids result in unique pharmacological profiles, which influence their efficacy and toxicity in both therapeutic and recreational settings (Fig. 1).

THC and CBD metabolism. THC and CBD are two of the most abundant phytocannabinoids found in *Cannabis sativa*, and they have distinct pharmacokinetic and metabolic profiles. Both compounds are highly lipophilic and are rapidly distributed in various tissues, including the brain and adipose tissue, after absorption. Their metabolism primarily occurs in the liver through the cytochrome P450 (CYP) enzyme system.

THC is predominantly metabolized in the liver by the CYP450 system, specifically by the CYP2C9, CYP2C19 and CYP3A4 enzymes. Upon administration, THC undergoes extensive first-pass metabolism, particularly when ingested orally, which significantly reduces its bioavailability (~4-12%) compared with inhalation (10-35%) (40). The major metabolic pathways of THC include hydroxylation and oxidation, producing the psychoactive metabolite 11-hydroxy-THC (11-OH-THC) and the inactive metabolite 11-carboxy-THC (THC-COOH). 11-OH-THC is known to retain psychoactive properties similar to THC itself and is rapidly formed after ingestion, reaching peak plasma concentrations within 13 min post-inhalation (41).

THC and its metabolites are primarily excreted through feces (65 to 80%), while ~20-35% is excreted through urine, mainly as conjugated metabolites (THC-COOH-glucuronide). Due to its lipophilicity, THC is stored in adipose tissues, leading to a prolonged elimination half-life of up to 13 days in chronic users (41).

CBD is metabolized primarily by CYP2C19 and CYP3A4, with subsequent involvement of CYP1A1, CYP1A2, CYP2C9 and CYP2D6 [Gonçalves *et al* (41)]. CBD undergoes

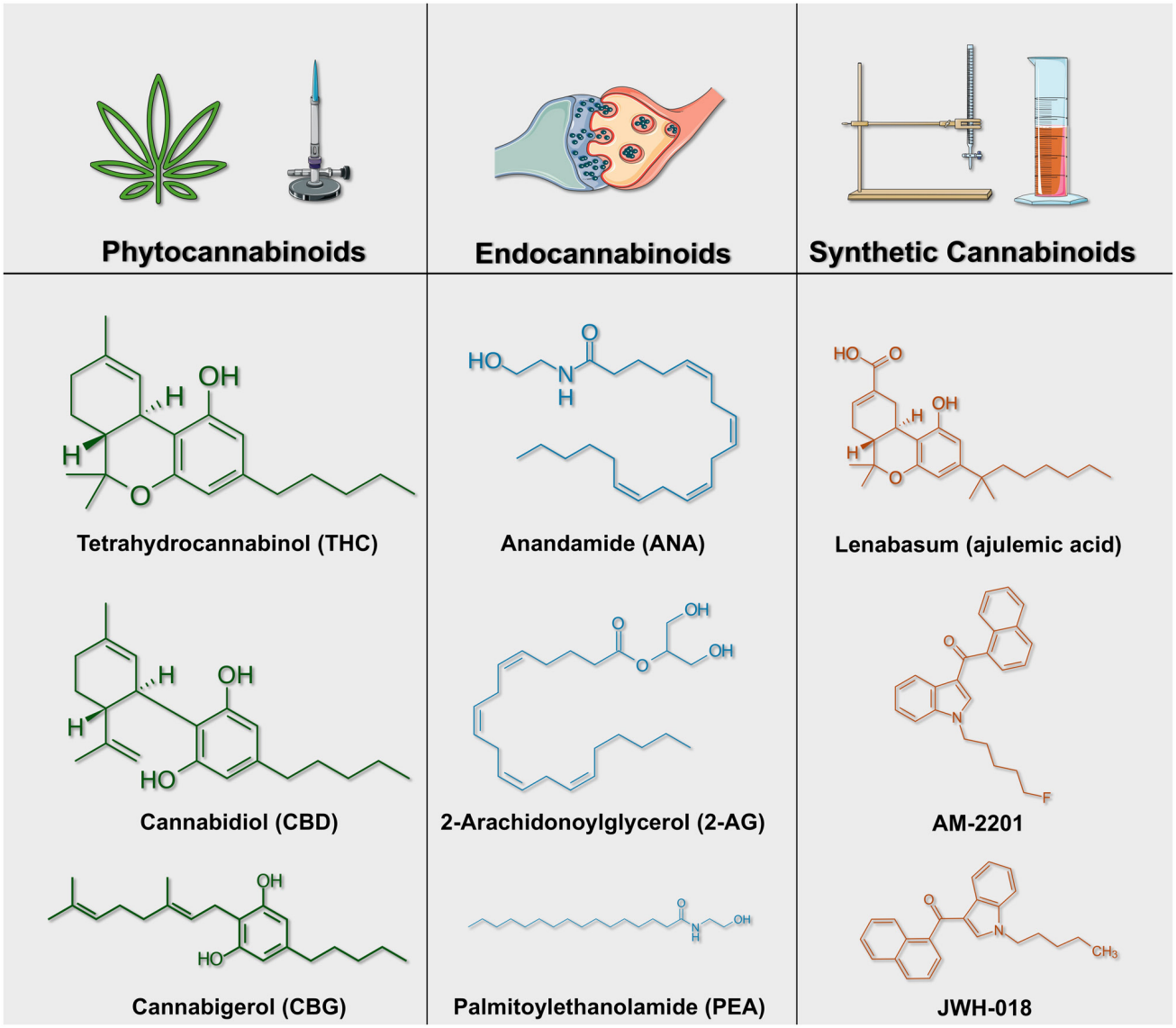

Figure 1. Chemical structures of common phytocannabinoids, endocannabinoids and synthetic cannabinoids. Parts of this image derived from the free medical site http://smart.servier.com/ (accessed on 15 March 2025) by Servier, licenced under a Creative Commons Attribution 4.0 Unported Licence.

hydroxylation and oxidation, forming major metabolites such as 7-hydroxy-CBD (7-OH-CBD) and its subsequent oxidized product 7-carboxy-CBD (7-COOH-CBD). Like THC, CBD exhibits low oral bioavailability (around 6%) due to extensive first-pass metabolism, while its inhalation bioavailability ranges from 11-45% (40).

CBD is primarily excreted in feces (60%) and to a lesser extent in urine (16%), mainly in the form of hydroxylated and carboxylated metabolites. The plasma half-life of CBD varies between 18-32 h (41).

Both THC and CBD are known to inhibit CYP enzymes, potentially leading to interactions with other medications metabolized by the same enzymes. CBD, in particular, is a potent inhibitor of CYP2C19 and CYP3A4, increasing the risk of drug interactions when co-administered with substrates of these enzymes (42). This interaction profile is clinically relevant, especially for patients on polypharmacy regimens, such as those receiving anticonvulsants or antiepileptic drugs (Fig. 2).

3. Patterns of cannabis consumption

Cannabis has been an integral component of human society for millennia, with archaeological and historical evidence suggesting that its use emerged independently in multiple regions. This pattern of emergence indicates a complex process of cultural exchange, particularly during the Bronze Age, when trans-Eurasian trade played a significant role in the globalization of cannabis, alongside the spread of other domesticated plants (43).

In contemporary society, cannabis use is pervasive, with data from the United States indicating that ~7.5% of individuals aged ≥12 years reported using marijuana in the preceding month as of 2013 (44). The prevalence of cannabis use has continued to increase, especially among adults, paralleling the legalization of medical and recreational cannabis in several states (44,45). The National Survey on Drug Use and Health has documented a consistent rise in cannabis consumption, reporting an increase in past-month cannabis use from 4.1% in

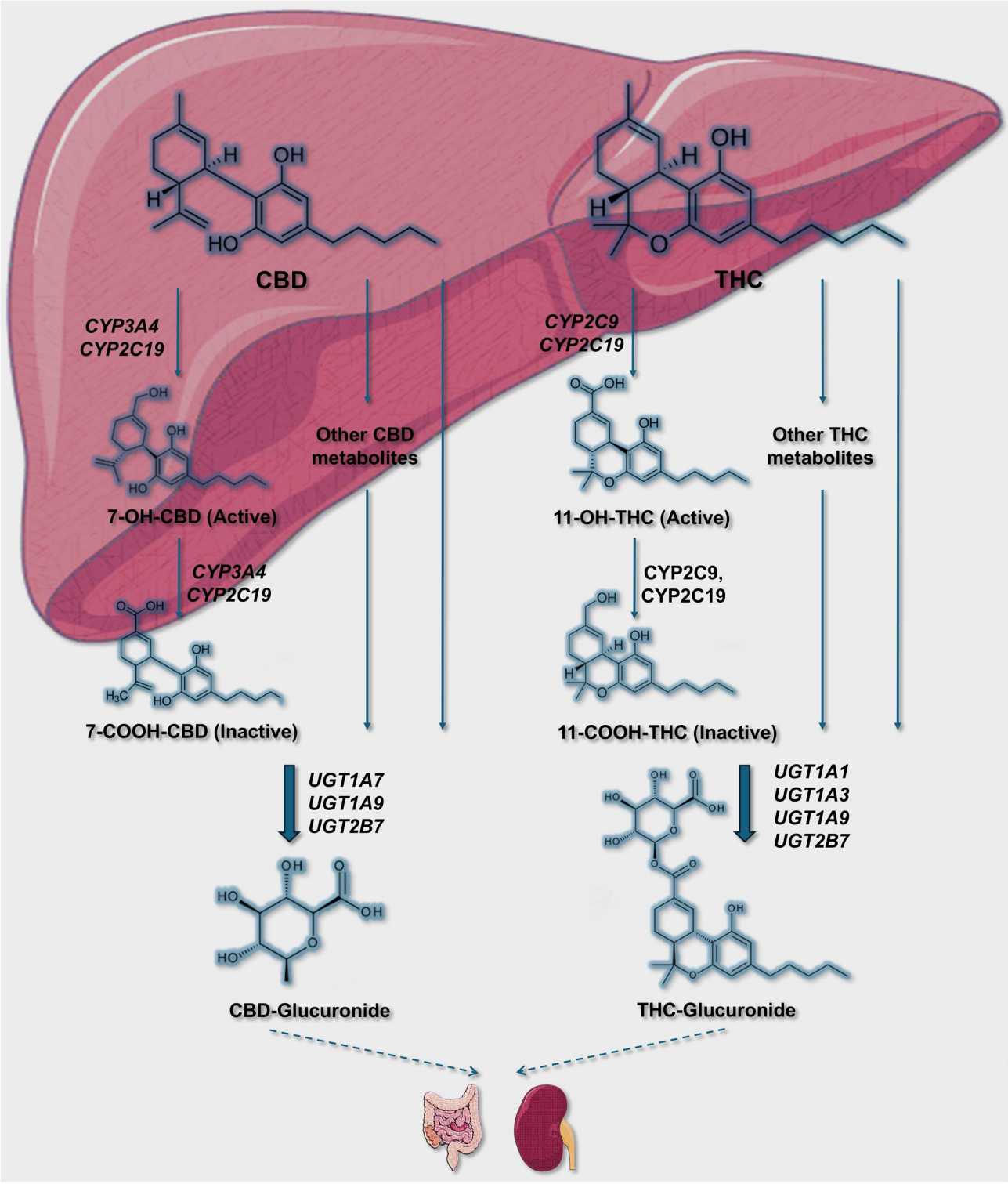

Figure 2. THC and CBD metabolism. Parts of this image derived from the free medical site http://smart.servier.com/ (accessed on 15 March 2025) by Servier, licenced under a Creative Commons Attribution 4.0 Unported Licence. THC, Δ-9-tetrahydrocannabinol; CBD, cannabidiol.

2001-2002 to 9.5% in 2012-2013 (28). Demographic analyses further reveal that cannabis use is more common among males, younger adults, and individuals residing in higher-income areas (44,45).

The shifting legal and social landscape surrounding cannabis has also contributed to increased use among older adults. For instance, there was a 57.8% relative increase in past-year cannabis use among adults aged 50-64 and a remarkable 250% increase among those aged 65 and older between 2006 and 2013 (46). This trend underscores the need for a comprehensive assessment of the long-term health implications of cannabis use across diverse age groups.

CUD, characterized by problematic cannabis consumption leading to significant impairment or distress, has emerged as a pressing public health issue. In Australia, it was reported that 6% of individuals experienced CUD within the past

12 months, with higher prevalence rates observed among males and younger users. Moreover, CUD has been strongly associated with other psychiatric conditions, including alcohol use disorders and affective disorders (47).

The legalization of recreational cannabis in various U.S. states, along with nationwide legalizations in countries such as Uruguay and Canada, has transformed patterns of cannabis consumption. Legalization has been associated with reduced prices, increased potency and enhanced accessibility of cannabis products. These changes have coincided with an increase in the frequency of cannabis use among adults and a rise in emergency department visits and hospitalizations related to cannabis-induced pathologies (48).

4. Mechanisms of cannabinoid activity

The physiological effects of cannabis are primarily mediated through the ECS, a complex network comprising cannabinoid receptors (CB1 and CB_2), endogenous cannabinoids (anandamide and 2-arachidonoylglycerol) and associated enzymes (39). The ECS plays a crucial role in regulating various central nervous system (CNS) and peripheral processes, including anxiety, depression, neurogenesis, cognition and memory (49).

THC, the principal psychoactive component of cannabis, exerts its effects primarily through CB1 receptors located in the CNS. By contrast, CBD interacts with a range of non-cannabinoid receptors and ion channels, modulating the psychoactive and physiological effects of THC. The biphasic nature of cannabinoid effects complicates the study of cannabis's impact on human health, as low doses may elicit effects that are opposite to those observed at higher doses (49).

Recent advances in ECS research have identified numerous endocannabinoid-like compounds within the brain that may influence a broad spectrum of brain functions, offering potential therapeutic targets for various neurological and psychiatric conditions (49). The intricate dynamics of the ECS underscore the complexity of cannabis's physiological effects, emphasizing the necessity for comprehensive investigations to unravel the mechanisms through which cannabis interacts with biological systems (15,49).

Cannabinoids exert their effects primarily through activation of the ECS, which consists of the cannabinoid receptors CB_1 and CB_2, endogenous ligands such as anandamide and 2-arachidonoylglycerol (2-AG), and enzymes responsible for ligand synthesis and degradation (50). CB_1 receptors are widely expressed in the CNS, where they regulate neurotransmitter release, cognition and reward pathways, but they are also found in peripheral tissues including the lungs, cardiovascular system and gastrointestinal tract (51). By contrast, CB_2 receptors are predominantly expressed on immune cells and modulate inflammation, immune surveillance and cytokine release (52,53).

Beyond receptor-mediated pathways, cannabinoids can influence a range of non-cannabinoid targets, including TRP channels, PPARs and serotonin receptors, which contribute to their complex physiological effects (19,54). In the respiratory system, CB_1 receptor activation can promote bronchial smooth muscle relaxation but also increases airway hyperreactivity with chronic exposure, while CB_2 signaling is implicated in modulating pulmonary inflammation and immune responses (32,54). At the cellular level, cannabinoids can alter oxidative stress, apoptosis and angiogenesis, processes relevant to both tissue injury and carcinogenesis (55,56).

Taken together, the mechanisms of cannabinoid activity are multifaceted, involving both central and peripheral CB_1/CB_2 receptor signaling as well as non-canonical pathways. This complexity underlies the dual potential of cannabinoids to provide therapeutic benefit in conditions such as chronic pain and multiple sclerosis while simultaneously contributing to adverse outcomes including cognitive impairment, immune dysregulation, and possibly increased cancer risk.

5. Cannabis composition and potency trends

A major determinant of the health impact associated with cannabis use is its potency, primarily dictated by the concentrations of THC, the principal psychoactive component, and CBD, a non-psychoactive constituent. Analysis of illicit cannabis samples seized by the U.S. Drug Enforcement Administration from 1995 to 2014 revealed a substantial increase in THC potency, rising from ~4% in 1995 to ~12% in 2014. Concurrently, CBD levels declined from ~0.28% in 2001 to less than 0.15% in 2014, resulting in a marked shift in the THC to CBD ratio from 14:1 to ~80:1 (57). This trend toward higher THC concentrations may be attributed to the cultivation of sinsemilla (seedless cannabis), favored for its potent psychoactive effects (57). Elevated THC levels are associated with more pronounced psychoactive effects, potentially increasing the risk of dependence, psychosis, and other adverse health outcomes (57,58). Moreover, the reduction in CBD content may diminish the mitigating effects of CBD on THC-induced anxiety and psychosis, thereby exacerbating the health risks posed by high-potency cannabis products (57). These compositional changes in cannabis underscore the need to reassess previous evidence and conduct contemporary studies that reflect current usage trends.

The increasing complexity of cannabis products, including the development of high-potency strains and synthetic cannabinoids, further complicates the evaluation of health risks. Synthetic cannabinoids, which frequently exhibit higher affinity for cannabinoid receptors than natural cannabis, can induce more intense psychoactive effects and are associated with severe adverse events (59). The interaction of various cannabinoid compounds, including THC and CBD, within the ECS adds another layer of complexity to understanding the nuanced health outcomes of cannabis use (49,58).

The relationship between use of cannabis and broader public health issues, such as the opioid epidemic, warrants critical consideration. Research has explored the potential role of cannabis as a substitute for opioids in pain management; however, findings remain inconclusive (47,60). Additionally, the co-use of cannabis with other substances, including alcohol and prescription medications, highlights the need to address polysubstance use within public health strategies (46,61). Notably, the existing literature often presents contradictory findings, partly due to methodological limitations such as small sample sizes, insufficient control for confounding variables, and variability in the potency and composition of cannabis products (62,63). Consequently, robust and methodologically

sound research is essential to accurately assess the health implications of contemporary cannabis use.

Over the last two decades, the average THC content in plant cannabis has increased substantially while CBD content has declined, driving a markedly higher THC:CBD ratio (16,57,58). This compositional shift has two broad implications. First, legacy epidemiology that used 'joint-years' to quantify exposure largely reflects low-potency eras; equal 'joint-years' today plausibly deliver far greater psychoactive dose and, depending on smoking topography, similar or greater particulate and PAH exposure per session. Consequently, null or weak associations from older cohorts (for example, pulmonary function plateaus at modest exposure) may underestimate modern risk (6,13,64).

Potency may also interact with behavior. Although users can partially titrate (for example, fewer puffs, shorter sessions), titration is imperfect and varies by experience, product type and setting, particularly with concentrates and high-efficiency devices. Thus, higher THC can increase delivered dose without proportionally reducing inhaled toxicants from combustion, maintaining exposure to tar and PAHs that drive airway inflammation and genotoxicity (6,24).

From a mechanistic perspective, rising THC with declining CBD could tilt airway biology toward a more pro-inflammatory milieu. CBD has documented anti-inflammatory and antiproliferative properties in experimental systems, whereas THC has complex, dose-dependent effects on immune function; a higher THC:CBD ratio may therefore attenuate any CBD-mediated modulation of THC's effects (14,16). Whether this compositional shift translates to higher lung cancer risk remains unsettled: Conventional observational studies are inconsistent and rarely stratify by potency, but Mendelian randomization (MR) analyses suggest a possible causal signal for lung cancer (and specifically squamous histology) with genetic liability to cannabis use/use disorder (65,66). Given that most case-control and cohort data were accrued in lower-potency periods and seldom capture THC concentration, extrapolating their null findings to contemporary high-THC markets is precarious.

Potency is also salient for non-combustible routes. High-THC concentrates delivered via vaporizers can markedly increase systemic THC without combustion by-products, but the EVALI outbreak-largely tied to adulterants in illicit THC cartridges-highlights distinct acute pulmonary hazards unrelated to THC potency *per se*; long-term oncologic effects of high-THC vapor exposures remain unknown (24,67).

In light of these trends, future studies should replace or complement 'joint-years' with dose-standardized metrics (for example, mg-THC-years), capture product THC and CBD content, device type, and co-use with tobacco, and analyze outcomes by potency strata. Mechanistic studies should employ modern high-THC smoke and aerosol models to test dose-response effects on airway inflammation, DNA damage and macrophage function (6,14).

6. Respiratory effects of cannabis use

Molecular impact of cannabis on lung cells. Understanding the molecular mechanisms underlying cannabis-induced pulmonary effects is essential to elucidating the pathways through which cannabis impacts lung pathophysiology. Cannabis smoke contains numerous toxic and carcinogenic compounds analogous to those present in tobacco smoke, raising significant concerns regarding its potential to induce deleterious effects on respiratory cellular architecture (68). Toxicogenomic analyses comparing the effects of tobacco and marijuana smoke condensates on murine lung epithelial cells have demonstrated that both types of smoke disrupt similar toxicological pathways, including xenobiotic metabolism, oxidative stress, inflammation and DNA damage response. However, marijuana smoke condensates exerted a more pronounced impact on steroid biosynthesis, apoptosis, and inflammation pathways, indicating distinct and potentially more aggressive molecular disruptions associated with cannabis smoke. Additionally, marijuana smoke exposure resulted in increased oxidative stress, which may contribute to the heightened cytotoxicity observed among cannabis smokers (69). These toxicogenomic findings underscore the unique and potentially more severe pulmonary impact of cannabis smoke compared with tobacco smoke.

Supporting these observations, a comprehensive analysis comparing the chemical composition of mainstream and sidestream cannabis smoke with that of tobacco smoke identified the presence of known carcinogens, including ammonia, hydrogen cyanide and PAHs, in cannabis smoke at concentrations comparable to or even exceeding those found in tobacco smoke. These findings raise significant concerns regarding the carcinogenic potential of cannabis, given the well-established association between tobacco smoke exposure and lung cancer (6).

To further investigate the molecular association between cannabis smoke and carcinogenesis, the DNA-damaging effects of cannabis smoke were examined by quantifying acetaldehyde-derived N_2-ethyl-2'-deoxyguanosine (N_2-ethyl-dG) adducts in DNA. This analysis revealed that exposure to cannabis smoke generated dose-dependent increases in DNA adducts, comparable to those induced by tobacco smoke. These findings strongly suggest the genotoxic potential of cannabis smoke, suggesting that chronic cannabis use could initiate carcinogenic processes similar to those observed with tobacco smoking (7).

In contrast to the evidence suggesting an oncogenic potential, cannabinoids have also demonstrated dual roles in both promoting and inhibiting tumorigenesis, depending on the specific context and molecular pathways involved. Phytocannabinoids and synthetic cannabinoids have exhibited antiproliferative effects on tumor cells *in vitro* and in some animal models. However, when considering the chronic inhalation of carcinogenic byproducts, immunosuppression, and sustained inflammation associated with cannabis smoke, any potential antitumor effects may be negated by the net mutagenic and growth-promoting environment (14). Consequently, the complex interplay between the pro- and anti-tumorigenic effects of cannabinoids warrants further investigation to delineate the potential health risks and therapeutic applications of cannabis use.

Immune modulation in cannabis smokers. In addition to the direct cytotoxic and genotoxic effects on epithelial cells, cannabis smoking alters lung immune homeostasis, leading to an inflammatory response and functional impairment of

alveolar macrophages (AMs), which play a critical role in airway surveillance and pathogen clearance. Chronic cannabis use has been associated with an inflammatory infiltrate within the lungs, reflecting chronic airway irritation and a potential predisposition to airway remodeling.

Investigations into the cellular composition of bronchoalveolar lavage (BAL) fluid in cannabis smokers revealed significantly elevated total cell counts, particularly neutrophils, in the BAL fluid of both marijuana-only and combined marijuana-tobacco smokers compared with non-smokers (49). This inflammatory cellular response may indicate chronic airway irritation and potential remodeling processes.

Further examination of airway inflammation through videobronchoscopy in young, healthy individuals who habitually smoked cannabis demonstrated significant airway inflammation, including vascular hyperplasia, submucosal edema and increased neutrophil counts. These inflammatory changes were comparable in frequency and magnitude to those observed in tobacco smokers, suggesting that cannabis smoke induces substantial airway inflammation similar to tobacco smoke (70).

In addition to airway inflammation, cannabis smoking has been shown to impair the function of AMs, which are essential for maintaining pulmonary immune defense. Functional assessments of AMs obtained from marijuana smokers demonstrated impaired phagocytosis and reduced fungicidal activity against *Candida albicans*, despite normal rates of ingestion of the pathogen (71). Furthermore, these macrophages exhibited diminished production of superoxide anions upon stimulation, a critical factor in microbial elimination (5,71).

Further investigations have also highlighted the diminished bactericidal activity of AMs from marijuana smokers, specifically against *Staphylococcus aureus*. In addition to impaired pathogen clearance, these macrophages exhibited reduced production of key pro-inflammatory cytokines, including tumor necrosis factor-alpha and interleukin-6, which are essential for orchestrating an effective immune response (72).

Cannabis smoking has been shown to impair the antimicrobial and immunomodulatory functions of AMs, thereby potentially increasing susceptibility to opportunistic infections and respiratory pathogens. One mechanistic basis for these impairments involves the suppression of nitric oxide (NO) production, a critical effector molecule in microbial defense. Research has demonstrated that cannabis use significantly reduces NO production in AMs, compromising their antimicrobial capabilities (73).

Further investigation into the functional consequences of reduced NO production revealed that AMs from marijuana smokers exhibited impaired bactericidal activity. This deficiency persisted unless the cells were primed with exogenous cytokines, indicating that cannabis-induced suppression of intrinsic cytokine priming mechanisms significantly hampers the antimicrobial efficacy of AMs (74). These findings suggest that chronic cannabis exposure may compromise the ability of AMs to eliminate ingested bacteria effectively, weakening pulmonary immune defense.

The immunologic impact of cannabis use extends beyond impaired NO production, with studies also exploring the epigenetic effects of Δ^9-THC on immune cells. Notably, research has demonstrated that THC induces histone modifications that shift cytokine gene expression from a T-helper 1 (Th_1) to a T-helper 2 (Th_2) profile. This epigenetic reprogramming may underlie the immunosuppressive effects observed in cannabis smokers, as the transition from a Th_1 to a Th_2 response is associated with impaired cytokine production and diminished antimicrobial activity of AMs (75). By altering the balance of Th_1 and Th_2 responses, THC may skew immune function toward a less effective state for combating infections and maintaining pulmonary homeostasis.

Collectively, these studies indicate that cannabis smoking could significantly impair the antimicrobial and immunomodulatory functions of AMs. This compromised immune function may increase vulnerability to respiratory infections and opportunistic pathogens, raising concerns about the long-term pulmonary health consequences of chronic cannabis use.

Structural and histopathologic impact. The persistent inflammatory state and immunological dysfunction induced by cannabis smoke are accompanied by distinctive structural and histopathological changes in the bronchial mucosa. Histopathological analyses have demonstrated that habitual marijuana smokers exhibit significant bronchial mucosal abnormalities, including goblet cell hyperplasia, vascular hyperplasia and cellular disorganization. These changes are indicative of chronic airway irritation and remodeling, which are known precursors to more severe respiratory diseases (76).

Moreover, the combination of marijuana and tobacco smoking appears to have additive detrimental effects on the bronchial mucosa. It has been demonstrated that habitual users of both substances experience more pronounced mucosal damage compared with those smoking either substance alone. Specifically, combined marijuana and tobacco smokers show higher frequencies of epithelial and submucosal alterations, suggesting that concurrent use exacerbates bronchial injury (76). This synergistic effect is particularly concerning given the high prevalence of dual use among cannabis and tobacco smokers, potentially amplifying the risk of severe airway damage and chronic respiratory conditions.

In addition to structural abnormalities, molecular and cellular alterations have been observed in habitual marijuana smokers. An investigation into bronchial biopsy specimens from a cohort of 104 volunteers, comprising non-smokers and habitual smokers of marijuana, tobacco, or both, revealed significant histopathological and molecular changes in cannabis users. Among individuals without lung cancer, habitual marijuana smokers displayed epithelial changes characterized by increased cellular proliferation markers, such as Ki-67, and elevated expression of the epidermal growth factor receptor. Additionally, abnormalities in DNA content were observed, suggesting early field cancerization changes akin to those seen in tobacco-exposed epithelium (77).

While the clinical implications of these findings remain uncertain, the presence of such molecular alterations raises concerns that habitual marijuana use may establish a pro-oncogenic microenvironment within the bronchial epithelium. This could potentially increase the risk of malignant transformation, especially when cannabis smoking is combined with tobacco use. Consequently, the synergistic impact of combined smoking on airway pathology highlights the importance of

further research into the long-term respiratory risks associated with dual substance use.

Structural lung changes associated with cannabis smoking have been investigated using high-resolution computed tomography (HRCT) scans. One study reported that cannabis smokers exhibited decreased lung density, which may reflect structural alterations such as airway wall thickening or early parenchymal changes (9). However, the prevalence of macroscopic emphysema among cannabis-only smokers was relatively low (1.3%) compared with significantly higher rates observed in combined cannabis and tobacco users (18.9%) and tobacco-only smokers (16.3%) (9). These findings suggest that while cannabis smoking may induce airflow obstruction and structural modifications, the development of emphysema likely requires higher exposure levels or the concurrent use of tobacco.

In addition to the structural changes observed on imaging, case reports have documented the occurrence of large bullae and spontaneous pneumothorax among heavy cannabis smokers, often at relatively young ages (78). Although large-scale epidemiological studies are yet to explore this association comprehensively, the presence of bullous disease in cannabis smokers raises concerns about localized overdistension and alveolar rupture. The chronic irritative and inflammatory environment associated with habitual cannabis smoking could lead to structural weaknesses in the alveolar walls, predisposing to bullous formations that are less commonly observed in non-cannabis users.

This distinctive pathological signature of cannabis-related lung damage warrants further investigation, as it may represent a unique manifestation of lung injury that differs from the well-documented effects of tobacco smoking. Understanding the mechanisms that predispose cannabis smokers to such changes will be crucial for identifying at-risk populations and implementing appropriate public health interventions.

7. Cannabis use and pulmonary function

Cannabis impact on lung physiology. Inhalation of cannabis smoke has been associated with numerous alterations in pulmonary function and respiratory health. Although both cannabis and tobacco combustion produce similar byproducts, the unique constituents of cannabis, particularly THC, may elicit distinct physiological responses within the pulmonary system, influencing airway physiology, airflow obstruction and long-term lung function.

A study analyzing data from the Tucson epidemiological study of airways obstructive disease demonstrated that among younger adults (under 40 years of age), smoking non-tobacco cigarettes (presumed primarily marijuana) was associated with increased respiratory symptoms and significant reductions in expiratory flow rates at low lung volumes. After adjusting for tobacco use, non-tobacco cigarette smokers, particularly men, exhibited decreases in the forced expiratory volume at 1 second (FEV_1) to forced vital capacity (FVC) ratio and flow rates that, in some instances, were even more pronounced than those seen in tobacco smokers. However, a limitation of that study was the characterization of non-tobacco cigarettes, which may have encompassed substances other than marijuana (11).

Further investigating this association, a study involving habitual heavy smokers of marijuana alone, those who smoked both marijuana and tobacco, tobacco-only smokers, and non-smokers found that marijuana smokers, regardless of concurrent tobacco use, reported significantly more respiratory symptoms, including cough, sputum production and wheezing. Habitual marijuana use was associated with decrements in specific airway conductance, indicating large airway obstruction (11). However, unlike tobacco smokers, these functional impairments did not consistently translate into a characteristic obstructive defect on spirometry, suggesting that cannabis may affect the airways differently from tobacco. This disparity may indicate that cannabis predominantly alters large airway caliber and reactivity rather than inducing small-airway remodeling.

Aldington *et al* (9) conducted a cross-sectional study in the Greater Wellington region of New Zealand to investigate the differential effects of cannabis and tobacco smoking. The study enrolled cannabis-only smokers, tobacco-only smokers, combined users and non-smokers, and employed comprehensive pulmonary evaluations, including HRCT scans, standard spirometry and a detailed respiratory questionnaire (9). A dose-response relationship was demonstrated between cannabis smoking and reductions in the FEV_1/FVC ratio, as well as decreased specific airway conductance and increased total lung capacity (9). The study reported that a single cannabis joint exerted a damaging effect on large airway function comparable to 2.5 to 5 tobacco cigarettes, though emphysema remained uncommon among cannabis-only users (9).

In addition, the Coronary Artery Risk Development in Young Adults (CARDIA) study, which followed U.S. adults for 20 years, found a nonlinear association between marijuana exposure and lung function. At low to moderate levels of use (for example, a few joints per month), modest but significant increases in FEV_1 and FVC were observed. However, with cumulative exposure beyond 10 joint-years, the slope became negative, and very heavy use (>20 uses per month) led to a slight decline in FEV_1 and a more notable increase in FVC, ultimately lowering the FEV_1/FVC ratio (13). This pattern indicates that while moderate cannabis use may not severely compromise lung function, excessive consumption may eventually result in airflow impairment.

Similarly, a cross-sectional study using data from the U.S. National Health and Nutrition Examination Survey (NHANES) found that lifetime marijuana use up to 20 joint-years did not adversely affect spirometry measures, including the FEV_1 and FEV_1/FVC ratio. However, exceeding 20 joint-years doubled the odds of an FEV_1/FVC ratio below 70%, suggesting that heavy, prolonged use might result in clinically significant airway obstruction (64). The study noted that changes in the FEV_1/FVC ratio were primarily driven by increases in FVC rather than pronounced declines in FEV_1, suggesting that cannabis might induce alterations in lung volume and elastic recoil distinct from the classical obstructive patterns observed with tobacco use (64).

Moreover, a study investigating the acute bronchodilator effects of cannabinoids on human bronchi demonstrated that cannabinoids inhibit cholinergic-induced bronchial contractions through CB_1 receptors, thereby providing a mechanistic explanation for the bronchodilation observed in cannabis

smokers. This finding underscores the role of cannabinoids in modulating airway tone by acutely relaxing bronchial muscles (10).

Collectively, these findings highlight the complex and multifaceted effects of cannabis on pulmonary function, ranging from acute bronchodilation to chronic airflow obstruction and structural changes, particularly with heavy and prolonged use. Further research is necessary to delineate the dose-dependent effects and long-term implications of cannabis inhalation on respiratory health.

Cannabis use and respiratory disorders. A study examining the association between cannabis use and chronic bronchitis symptoms found that current marijuana use was significantly linked to an elevated prevalence of chronic bronchitis, coughing, phlegm production and wheezing. By controlling for variables such as asthma, age, sex and tobacco use, the study demonstrated that the association between cannabis use and bronchitic symptoms remained independent and robust (12).

Further exploring the respiratory effects of cannabis, a longitudinal study evaluated respiratory symptoms in a population-based cohort of 1,037 young adults assessed at ages 18, 21, 26, 32 and 38 (79). Frequent cannabis use (defined as ≥52 times in the past year) was associated with chronic bronchitic symptoms, including morning cough, sputum production, and wheeze. Notably, these symptoms either resolved or significantly diminished when individuals discontinued or substantially reduced cannabis intake (79). This finding suggests that cannabis-related bronchitic changes may primarily result from inflammatory or irritative processes rather than fixed structural damage, as evidenced by the reversibility of symptoms upon cessation.

Together with findings from additional studies, these results indicate that cannabis, similar to tobacco, exerts irritant effects on the airways that clinically manifest as chronic bronchitis-like symptoms. However, the mechanisms underlying these effects may differ, given the potential for symptom resolution with reduced cannabis exposure.

Furthermore, a study assessing the risk of chronic obstructive pulmonary disease (COPD) in relation to cannabis use found that while smoking tobacco alone was associated with an increased risk of COPD and respiratory symptoms, cannabis use alone did not significantly elevate COPD risk (74). However, individuals who smoked both tobacco and cannabis exhibited a synergistic effect, with the risk of COPD and symptom burden being greater than what would be expected from tobacco smoking alone. This compounded risk was particularly pronounced at higher cumulative cannabis exposure levels (>50 joints lifetime) (80).

These findings suggest that although cannabis use alone may not significantly increase the risk of developing COPD, the concurrent use of tobacco and cannabis can lead to an augmented risk. The synergy between the two substances warrants caution, especially in populations with high rates of dual use. Moreover, the apparent reversibility of bronchitis symptoms associated with cannabis cessation highlights the potential for mitigating respiratory harm through reduction or discontinuation of cannabis use.

Comparative respiratory effects of cannabis and tobacco. Numerous studies have compared the effects of cannabis and tobacco on lung health outcomes, highlighting both similarities and differences in their physiological impacts. Although both substances share common inhalational byproducts, they differ significantly in the mechanisms and outcomes of respiratory impairment.

One study reported that cannabis smoking induces significant airflow obstruction, albeit with distinct structural consequences compared with tobacco (9,81). While cannabis smoking was consistently associated with reductions in the FEV_1/FVC and specific airway conductance, the prevalence of macroscopic emphysema remained relatively low unless cannabis use was combined with tobacco smoking (9). By contrast, tobacco smoking is strongly linked to both large and small airway dysfunction and significantly higher rates of emphysema (9,81). Notably, marijuana smoking impairs large airway function but does not accelerate the decline in FEV_1 over time as tobacco smoking does (11). This differential impact suggests that the pathophysiological mechanisms underlying cannabis- and tobacco-induced lung damage may diverge, with cannabis primarily affecting airway conductance and tobacco contributing more broadly to both obstructive and restrictive lung disease.

Further evidence highlights the synergistic respiratory risks associated with concurrent cannabis and tobacco use. Studies have demonstrated that dual use of these substances markedly increases the risk of respiratory symptoms and COPD beyond what would be expected from tobacco smoking alone (73,80). This synergy may result from cumulative exposure to inhaled toxins, compounded inflammatory responses, or overlapping detrimental effects on airway architecture and immune function.

Overall, cannabis use consistently emerges as a risk factor for chronic bronchitis symptoms, airflow obstruction and immunological dysregulation. However, unlike tobacco, cannabis use does not uniformly lead to emphysema or progressive declines in FEV_1, suggesting differing underlying mechanistic pathways. Nonetheless, the established synergy between cannabis and tobacco underscores the importance of integrated public health strategies that address dual substance use.

To comprehensively elucidate the causal pathways and individual susceptibilities associated with cannabis-related lung damage, large prospective cohort studies are needed. These studies should employ standardized cannabis exposure metrics and rigorously control for confounding factors, including tobacco use and pre-existing respiratory conditions. Additionally, molecular and mechanistic studies are warranted to explore how cannabis smoke specifically affects airway structure and function compared with tobacco, which could inform targeted interventions and harm reduction strategies.

Several longitudinal and case-control studies have directly compared the respiratory effects of cannabis and tobacco. In the Dunedin Multidisciplinary Health and Development Study, cumulative cannabis use was associated with increased FVC but no consistent decline in FEV_1, contrasting with the clear dose-dependent FEV_1 decline observed in tobacco users (79). The CARDIA cohort similarly reported that low-to-moderate cannabis exposure was associated with modest increases in FEV_1 and FVC, though heavy cumulative use attenuated these benefits, whereas tobacco demonstrated progressive declines

in both parameters (13). In a New Zealand case-control study incorporating HRCT, emphysema and reduced specific airway conductance were more strongly linked to tobacco than to cannabis, although dual users experienced the greatest impairment, suggesting possible additive or synergistic effects (9).

Cannabis and tobacco also differ in their effects on bronchitic symptoms and emphysema. Regular cannabis use has been consistently associated with chronic bronchitis symptoms, including cough, phlegm and wheeze (12,82). These symptoms often remit after cessation of cannabis use, whereas tobacco-related bronchitic changes typically persist (82). Imaging studies have found cannabis smoking to be associated with airway-centered emphysema, though with lower frequency than tobacco-associated emphysema (83). Tobacco smoking remains the dominant risk factor for emphysema and COPD, but the combined use of cannabis and tobacco appears to exacerbate respiratory symptoms and structural damage (9,83).

Cancer risk comparisons also reveal divergent patterns. While tobacco smoking is an established carcinogen with a clear dose-response relationship to lung cancer, the evidence for cannabis is more mixed. A large case-control study in Los Angeles reported no significant association between cannabis use and lung or upper aerodigestive tract cancers after adjustment for tobacco (8). By contrast, a New Zealand case-control study found an increased risk of lung cancer associated with heavy cannabis use, with an exposure-response trend (84). More recently, MR analyses have provided genetic evidence for a possible causal relationship between cannabis use and lung cancer, particularly squamous cell carcinoma (65,66). These findings suggest that, while tobacco remains the far stronger driver of malignancy, heavy cannabis exposure may not be benign with respect to cancer risk.

8. Cannabis and lung cancer risk

The potential association between cannabis inhalation and lung cancer risk has become increasingly relevant in the context of evolving legalization and rising global usage. Although cannabis smoke shares carcinogens with tobacco smoke, epidemiological findings regarding lung cancer risk remain inconclusive and complex. Confounding factors such as tobacco co-use and challenges in accurately quantifying lifetime cannabis exposure, often due to its legal status, further complicate the investigation.

A large retrospective cohort study within the Kaiser Permanente health system in California, involving 64,855 individuals, reported no significant association between overall cannabis use and cancer incidence, including lung cancer, after adjusting for sociodemographic factors and tobacco use (85). However, the study noted site-specific associations, particularly an elevated risk of prostate cancer among non-tobacco smokers who used cannabis and a near-significant increase in cervical cancer risk. These findings suggest that while overall cancer risk may not be markedly elevated, cannabis use could predispose to specific cancer types (85).

Similarly, a population-based case-control study in Los Angeles, encompassing 1,212 incident cancer cases and 1,040 controls, initially indicated a positive association between heavy cannabis use (>30 joint-years) and various cancer types, including lung cancer. However, after adjusting for confounders such as cigarette smoking, these associations were no longer significant, with an adjusted odds ratio (OR) for lung cancer of 0.62 [95% confidence interval, (CI): 0.32-1.2] among individuals with ≥60 joint-years of cannabis use, indicating no significant association (8).

Conversely, a case-control study conducted in New Zealand demonstrated a dose-response relationship between cannabis use and lung cancer risk, reporting an 8% increase in lung cancer risk per joint-year of cannabis smoking (95% CI: 2-15%) after adjusting for tobacco smoking. Notably, individuals in the highest tertile of cannabis use exhibited a significantly elevated risk [relative risk (RR)=5.7; 95% CI: 1.5-21.6] (84). Another hospital-based case-control study in Tunisia, involving 149 incident lung cancer cases and 188 controls, found a significant association between past cannabis use and lung cancer risk, with an OR of 4.1 (95% CI: 1.9-9.0) after accounting for age, tobacco use and occupational exposures (66). However, the study did not identify a clear dose-response relationship regarding the intensity or duration of cannabis use (87).

Further supporting this association, a pooled analysis of three hospital-based case-control studies conducted in Tunisia, Morocco and Algeria, involving 430 lung cancer cases and 778 controls, demonstrated an adjusted OR of 2.4 (95% CI: 1.6-3.8) for cannabis smoking after adjusting for country, age, tobacco smoking and occupational exposure (87). Although the study observed an increasing risk with joint-years of use, it did not identify a clear dose or duration relationship (65). Importantly, all cannabis smokers in this cohort were also tobacco users, raising concerns about residual confounding by tobacco or other factors (87).

In a longitudinal cohort study conducted over 40 years, involving 49,321 young men in Sweden, heavy cannabis use (defined as more than 50 lifetime uses) was associated with a more than two-fold increase in lung cancer risk [hazard ratio (HR)=2.12; 95% CI: 1.08-4.14] after controlling for confounders such as tobacco use, alcohol consumption, respiratory conditions and socioeconomic status (88). The large sample size, extended follow-up period, and robust adjustment for confounders strengthen the validity of these findings.

MR studies have also provided insights into the potential causal relationship between cannabis use and lung cancer. One MR study assessing the relationship between genetic liability to cannabis use and lung cancer susceptibility reported a significant association with squamous cell carcinoma (OR=1.22; 95% CI: 1.07-1.39; P=0.003) (65). Another MR analysis found that CUDs were linked to an increased risk of both breast cancer (OR=1.007; P=0.007) and lung cancer (OR=1.122; P=0.014) (66). MR studies have the advantage of reducing confounding and reverse causation biases inherent in observational designs, though they rely on the validity of genetic instruments.

The convergence of evidence from these studies suggests a potential link between heavy cannabis use and increased lung cancer risk, particularly when usage exceeds critical thresholds or is combined with tobacco smoking. The potential dose-response relationship observed in several studies underscores the importance of moderating heavy and chronic cannabis use to mitigate cancer risk.

However, methodological challenges persist, including confounding by tobacco use, variability in cannabis potency and consumption patterns, and limitations in accurately measuring exposure. Future research should prioritize prospective cohort studies with comprehensive exposure metrics and meticulous control for confounding variables, including occupational and environmental factors. Additionally, mechanistic studies exploring the biological underpinnings of cannabis-induced carcinogenesis are warranted to elucidate the pathways through which cannabis inhalation may contribute to cancer development.

A major limitation across the literature is residual confounding from tobacco, given the high prevalence of dual use and the collinearity of exposure metrics (pack-years, depth of inhalation, and mixing practices such as 'blunts' and tobacco-mixed joints). Even with statistical adjustment, under-reporting of tobacco, imprecise pack-year quantification, and differing smoking topography can bias risk estimates toward the null for cannabis or inflate apparent cannabis risks (62). Evidence for interaction is most apparent in structural and functional lung outcomes: In a comprehensive HRCT/physiology study from New Zealand, emphysema was uncommon among cannabis-only users but more frequent in tobacco-only smokers and highest in dual users, consistent with at least additive-if not synergistic-effects on airway and parenchymal injury (9). Symptom-based studies likewise show greater bronchitic burden when cannabis and tobacco are combined (12).

Whether any studies adequately isolate cannabis-specific risks depend on outcome and design. Several pulmonary studies enrolled cannabis-only groups and demonstrate large-airway dysfunction and symptomatology independent of tobacco (9,11), while population cohorts show non-linear lung-function patterns with cannabis exposure after tobacco adjustment (13) and increased odds of airflow obstruction at very high lifetime use (64). For lung cancer, findings remain mixed: Large case-control work from Los Angeles reported no association after adjusting for tobacco (8), whereas a New Zealand study suggested an exposure-response increase in risk per joint-year despite adjustment (84). Studies from North Africa are difficult to interpret because nearly all cannabis users also smoked tobacco, making cannabis-specific effects inseparable (87). A long-term Swedish cohort observed higher lung-cancer risk in very heavy cannabis users after controlling for tobacco and other confounders, though residual bias cannot be excluded (88). Notably, MR analyses-less sensitive to confounding-support a possible causal signal for lung cancer (including squamous histology) with genetic liability to cannabis use/use disorder, but these approaches have their own assumptions and do not capture route, dose, or combustion exposures (65,66).

Methodologically, future studies should i) recruit never-tobacco smokers to derive cannabis-only estimates; ii) verify tobacco exposure with biomarkers (for example, cotinine) alongside detailed cannabis metrics (product potency, device, mg-THC-years); iii) model additive and multiplicative interaction between cannabis and tobacco with formal measures of synergy; and iv) triangulate observational findings with modern experimental smoke/aerosol models that reflect contemporary high-THC products (6,62).

Findings on dose-response relationships between cannabis use and respiratory outcomes are inconsistent. Some studies suggest a threshold effect, with minimal impairment at lower exposures but measurable declines beyond ~20 joint-years. In the CARDIA cohort, low-to-moderate cannabis use was associated with transient increases in FVC, while heavier cumulative use predicted declines in FEV_1/FVC (13). Similarly, an analysis of NHANES data found increased odds of airflow obstruction when exposure exceeded 20 joint-years (64). By contrast, other studies have not identified a clear threshold, reporting either preserved or increased FVC despite high cumulative exposure (89) or mixed associations with spirometry and imaging markers (9). A systematic review and meta-analysis also highlighted the variability across studies, finding consistent links with bronchitic symptoms but less uniform associations with lung function decline (62).

These inconsistencies may partly reflect methodological heterogeneity. The 'joint-years' metric fails to capture differences in potency, device efficiency, or smoking topography, while secular increases in THC and shifts in the THC:CBD ratio complicate comparisons with earlier cohorts (57). Residual confounding from tobacco use, differences in modeling exposure categories vs. continuous measures, and survivorship bias in heavy users further cloud interpretation (6,9). Nonetheless, true biological non-linearity is also plausible: Acute bronchodilation and hyperinflation effects at low exposure may transiently mask airway obstruction, with chronic inflammation and remodeling emerging at higher doses (10). For lung cancer, some case-control studies found no dose-response gradient after tobacco adjustment (8), whereas others reported elevated risks with heavy cannabis use (84), and MR studies suggest a potential causal link, particularly with squamous histology (65,66).

Beyond epidemiological associations, several mechanistic studies provide biological plausibility for a link between cannabis use and lung cancer. Cannabis smoke contains numerous of the same carcinogens and mutagens as tobacco smoke, including PAHs and nitrosamines, often at equal or higher concentrations due to the combustion process and inhalation technique (6). Regular cannabis users typically inhale more deeply and hold smoke longer in the lungs, which may increase exposure of airway epithelium to carcinogens (90).

At the cellular level, cannabis smoke has been shown to induce DNA damage, chromosomal aberrations, and impaired DNA repair in human lung epithelial cells (91). *In vivo* studies demonstrate that marijuana smoke exposure disrupts mitochondrial function and promotes oxidative stress, which can accelerate carcinogenic pathways (91). Histopathological investigations have revealed squamous metaplasia, atypia and dysplasia in bronchial biopsies from habitual cannabis smokers, mirroring precancerous changes observed in tobacco smokers (77).

Interestingly, cannabinoids themselves may have dual roles. THC and CBD have demonstrated anti-proliferative and pro-apoptotic effects against certain tumor cell lines, suggesting potential anti-cancer properties (56). However, chronic exposure through smoking may overwhelm these effects due to the high burden of combustion-derived carcinogens. Thus, the balance between cannabinoid-mediated tumor suppression and smoke-induced carcinogenesis remains unresolved.

These mechanistic observations underscore that cannabis smoking is not biologically inert and can contribute to molecular changes associated with lung carcinogenesis.

9. Clinical implications

Clinical implications of cannabis use on lung health and cancer risk are multifaceted and warrant careful consideration, particularly in light of its increasing prevalence due to legalization and social acceptance. Chronic cannabis smoking has been associated with respiratory symptoms similar to those observed in chronic bronchitis, including cough, sputum production and wheezing. Notably, these symptoms appear to be reversible upon cessation of cannabis use, suggesting that the primary mechanism may be related to airway irritation and inflammation rather than irreversible lung damage (92).

Pulmonary function may not be significantly impaired with moderate cannabis use, but heavy and prolonged consumption has been linked to airflow obstruction and altered lung volumes. Unlike tobacco smoking, cannabis appears to primarily affect large airway caliber without consistently inducing small-airway remodeling or emphysema. However, the concurrent use of tobacco and cannabis has synergistic effects, amplifying the risk of chronic bronchitis, COPD and airflow obstruction beyond what would be expected from tobacco use alone (9,89).

In terms of oncological concerns, the risk of lung cancer associated with cannabis smoking remains inconclusive. Despite the presence of carcinogens similar to those found in tobacco smoke, epidemiological studies have not consistently demonstrated a strong association between cannabis use and lung cancer. Emerging evidence suggests that heavy, long-term cannabis use may increase lung cancer risk, especially when combined with tobacco smoking. Potential carcinogenic mechanisms involve exposure to harmful compounds such as PAHs and VOCs, which can induce DNA damage, oxidative stress and chronic inflammation-key processes involved in carcinogenesis. Furthermore, cannabinoids like THC and CBD have shown both tumor-promoting and antineoplastic properties in experimental models, yet the chronic inhalation of smoke may counteract any potential protective effects by fostering a mutagenic environment (9,88).

Immunological and infectious risks are also noteworthy, as chronic cannabis smoking has been shown to impair the antimicrobial functions of AMs, reducing phagocytic activity and NO production. This suppression may increase susceptibility to respiratory infections and opportunistic pathogens, with altered cytokine profiles and impaired antimicrobial activity weakening pulmonary immune defense. These effects may be particularly concerning among heavy users or those who concurrently smoke tobacco (72,93).

From a public health perspective, it is crucial to educate patients about the potential respiratory risks associated with chronic cannabis use, especially those with pre-existing respiratory conditions or who practice dual substance use. Implementing harm reduction strategies, such as recommending alternatives to smoking such as vaporization or oral formulations, could mitigate the inhalation of harmful byproducts. Additionally, regular monitoring for respiratory symptoms and lung function assessment should be considered for heavy cannabis users, particularly those with a history of tobacco use.

Beyond smoking, alternative routes of cannabis administration such as vaping and oral ingestion present distinct implications for lung health. Smoking remains the most strongly associated with respiratory symptoms including cough, sputum production, wheeze and bronchitic changes, as well as structural airway alterations and airflow obstruction (9,11). Vaping reduces exposure to combustion-related toxins such as tar and PAHs, which may lower certain toxicological risks (6,62). However, emerging data highlight important safety concerns. Vaping has been associated with airway irritation, bronchitic symptoms and impaired pulmonary function in young adults (94), and the outbreak of e-cigarette or EVALI underscored the risk of acute, severe pulmonary damage, largely linked to additives such as vitamin E acetate in illicit cartridges. By contrast, oral formulations-including edibles and oils-bypass the respiratory tract and therefore avoid combustion- and inhalation-related injury. Nevertheless, oral use is associated with delayed onset, variable absorption, and risks of overconsumption due to unpredictable pharmacokinetics (25). Taken together, smoking carries the greatest burden of chronic bronchitic and structural respiratory effects, vaping may reduce some combustion-related harms but introduces risks of acute lung injury and uncertain long-term consequences, while oral routes minimize pulmonary risks but raise challenges related to dosing and psychoactive effects.

Further research is essential to address the existing gaps, particularly through robust longitudinal cohort studies that assess the dose-response relationship between cannabis use and lung cancer risk. Modern high-potency cannabis products and changing patterns of consumption require contemporary investigations to improve understanding of the long-term consequences. Moreover, mechanistic studies exploring the molecular pathways through which cannabis smoke induces lung damage and carcinogenesis are needed to provide more comprehensive insights. Finally, public health policies should prioritize strategies to reduce dual substance use, given the compounded respiratory risks associated with the concurrent consumption of cannabis and tobacco.

10. Strengths and limitations

Several reviews have previously summarized the respiratory and oncological consequences of cannabis use, underscoring its association with bronchitic symptoms, impaired lung function and potential links to carcinogenesis (95-105). While these reviews have contributed significantly to understanding cannabis-related pulmonary risks, most either focused primarily on epidemiological associations or on narrower clinical outcomes, without integrating the increasing body of mechanistic, immunological and histopathological evidence. Furthermore, the majority of earlier reviews were based on data from periods when cannabis potency was considerably lower than in contemporary markets, with fewer analyses accounting for the impact of the rising THC to CBD ratio.

By contrast, the present review seeks to provide an updated and integrative perspective by combining epidemiological evidence with mechanistic insights into airway inflammation, alveolar macrophage dysfunction, and carcinogen-mediated

DNA damage. Particular emphasis was also placed on dual cannabis-tobacco use and its synergistic effects on chronic bronchitis, airflow obstruction and cancer risk, a dimension that remains underexplored in prior syntheses. Importantly, our review incorporates the most recent literature, including large-scale longitudinal studies, systematic reviews, and MR analyses recently published, thereby offering a timely reassessment of the pulmonary and oncological consequences of cannabis in the context of increasing legalization, higher product potency, and evolving consumption patterns. This comprehensive approach distinguishes the current review from earlier publications and provides clinicians and policymakers with a more contemporary framework for evaluating the health impacts of cannabis use.

11. Conclusions

While cannabis smoking is associated with respiratory symptoms resembling chronic bronchitis and impaired alveolar macrophage function, the link between cannabis use and lung cancer remains inconclusive, with conflicting epidemiological evidence. Moderate cannabis use does not appear to significantly impair pulmonary function, but heavy and prolonged consumption may lead to airflow obstruction and increased lung volume without causing emphysema as observed with tobacco smoking. Additionally, the combination of cannabis and tobacco use poses synergistic risks, amplifying respiratory and possibly oncogenic outcomes. While non-combustible methods such as vaping have been proposed as harm reduction strategies, they are not without risks. Compared with smoking, vaping cannabis eliminates some combustion-related toxins, such as PAHs and tar and may therefore reduce direct exposure to certain carcinogens. However, vaping introduces its own safety concerns, particularly with the emergence of e-cigarette or EVALI, largely linked to vitamin E acetate and other additives in illicit cartridges. Studies have described acute lung injury, hypoxemia, and even fatalities associated with vaping-related toxicity. Moreover, the high bioavailability of THC through vaping can encourage more intense use, potentially exacerbating dependence and neurocognitive risks. Thus, although vaping may mitigate some harms associated with smoke inhalation, it does not represent a risk-free alternative. A critical comparison indicates that while smoking carries stronger associations with chronic bronchitis, airflow obstruction and potential oncogenesis, vaping raises concerns of acute pulmonary toxicity and long-term safety uncertainties. Therefore, both methods warrant careful public health evaluation rather than unqualified endorsement as safer consumption routes.

As cannabis legalization expands and consumption patterns evolve, further longitudinal studies are essential to clarify the long-term health impacts and guide public health strategies aimed at harm reduction and safer use practices.

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DAA and VEG conceptualized the study. VEG, DAA, WZ and DAS made a substantial contribution to data interpretation and analysis and wrote and prepared the draft of the manuscript. WZ and VEG analysed the data and provided critical revisions. All authors contributed to manuscript revision, read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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