swiss medical weekly

Review article: Biomedical intelligence | Published 01 July 2025 | doi:https://doi.org/10.57187/s.4346
Cite this as: Swiss Med Wkly. 2025;155:4346

Caffeine, nicotine, cannabis, and psilocybin: Pharmacology, toxicology, and potential therapeutic uses of four naturally occurring psychoactive substances

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Summary

Psychoactive substances are compounds that can influence perception, consciousness, cognition, and emotions. The psychoactive substances caffeine, nicotine, cannabis, and psilocybin all originate from natural sources and can be used without complex processing or synthesis. Their natural availability has contributed to a long-standing history of human use and cultural significance. Caffeine and nicotine are freely available and commonly used as everyday stimulants, whereas psilocybin is more strictly regulated and cannabis has been legalised in some countries and regions. Some of these substances have been intensively studied, and their pharmacological and toxicological properties are well known, but ongoing research continues to investigate their therapeutic use for specific diseases and disorders. This narrative review aims to provide an overview of the pharmacology and toxicology of these four naturally occurring psychoactive substances, including a summary of the currently available evidence on their therapeutic potential, health benefits, and associated risks.

Introduction

Psychoactive substances exert their effects on the central nervous system, influencing perception, mood, emotions, consciousness, cognition, and behaviour [1]. These substances fall broadly into two categories: synthetic compounds and those derived from natural sources. While naturally occurring substances are sometimes viewed as "healthier" by users, the origin generally does not influence the toxicological properties. Caffeine, nicotine, cannabis, and psilocybin are all naturally occurring psychoactive substances and have long-standing sociocultural significance. However, their regulatory frameworks vary considerably, from caffeine and nicotine being readily available and integrated into many daily routines to the more stringent regulations surrounding cannabis and psilocybin.

Nicotine, primarily found in tobacco, has been intensely studied because of its strong dependence liability and the deleterious effects associated with tobacco smoking. Caffeine is a global mainstay of daily routines because of its productivity-enhancing and attention-increasing effects. Cannabis has recently garnered heightened attention because of its potential beneficial effects and its evolving legal status [2]. Similarly, psilocybin has sparked a lot of interest as a potential therapeutic agent in challenging-to-treat conditions like depression and anxiety disorders [3, 4]. All these substances – nicotine, caffeine, cannabis and psilocybin – have a generally favourable safety profile, increasing their attractiveness as potential therapeutic options for specific conditions.

This narrative review aims to provide an overview of the current understanding and available data on four selected natural psychoactive substances (two commonly used in everyday life, i.e. caffeine and nicotine, and two with varying regional regulations, i.e. cannabis and psilocybin) that have gained increasing interest because of their potential therapeutic uses in recent years. We highlight current therapeutic applications and discuss evidence pointing towards potential novel uses.

ABBREVIATIONS

5-HT:	serotonin
cAMP	cyclic AMP
CB:	cannabinoid receptor
CBD:	cannabidiol
CBN:	cannabinol
CYP:	cytochrome P450 enzymes
LSD:	lysergic acid diethylamide
MAO:	monoamine oxidase
THC:	Δ9-tetrahydrocannabinol
TRPV1:	transient receptor potential vanilloid 1

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Caffeine

Caffeine, or 1,3,7-trimethylxanthine, is a naturally occurring alkaloid found in the beans of, for example, the Arabica coffee plant and more than 60 other plants [5–7]. It is the most commonly used psychostimulant worldwide, with its consumption going back thousands of years [6, 8–10]. Caffeine is typically consumed in the form of beverages, such as coffee, tea, and soft drinks, but can also be found in chocolate and in various prescription and over-the-counter (OTC) drugs and supplements [5, 6, 9]. Depending on the preparation, an espresso coffee can contain approximately 100 mg and a cup of tea 40–60 mg of caffeine, while larger amounts can be found in energy drinks [11]. Caffeine is also commonly found as an adulterant in illicit recreational drugs, sometimes in concentrations high enough to cause acute caffeine toxicity [12].

Pharmacokinetics

After oral intake, caffeine, a weak base with bioavailability of almost 100%, is rapidly absorbed with peak concentrations reached within 30–60 minutes without food [6, 7]. Due to its lipophilic nature, caffeine can readily cross cell membranes, including the blood-brain barrier. In adults, the volume of distribution is 0.6–0.8 L/kg and binding to protein is low (approximately 35%) [7, 9]. Serum concentrations in coffee drinkers are typically in the range of 1–10 mg/l [9]. Caffeine's metabolism is rather complex, with more than 25 metabolites identified so far and some cytochrome P450 enzymes (CYP) being involved only at high concentrations [6]. Caffeine is primarily metabolised in the liver, mainly by CYP1A2. The main metabolite after demethylation is paraxanthine (80%); other metabolites involving CYP1A2, but also CYP2E1, include theobromine (11%) and theophylline (5%) [6, 7]. Further metabolism by CYP1A2, as well as N-acetyltransferase, xanthine oxidase or CYP3A4, leads to further metabolites that are primarily excreted in the urine [6]. Due to genetic polymorphisms and potential interactions with other substances, the rate of metabolism varies widely across individuals, and the elimination half-life can range between 3 and 10 hours (usually 4–6 hours in healthy adults; prolonged in newborn infants and in the elderly) [7, 9, 13]. In adults, less than 5% is eliminated unchanged in the urine [6, 7], while urinary concentrations of >12 mg/l used to be considered doping in sports before the removal of caffeine from the list of banned substances [14]. After oral consumption of 100 mg, caffeine is found in the milk of breastfeeding women at concentrations of ~2–4 mg/l [15], but consumption of moderate amounts during breastfeeding is considered safe [16]. Caffeine crosses the placenta, and its elimination half-life is prolonged during pregnancy [17, 18].

Pharmacodynamics

The effects of caffeine are mainly mediated by the nonselective antagonism of adenosine. Caffeine in high concentrations inhibits phosphodiesterase, which can result in increased concentrations of cyclic AMP (cAMP). This can lead to a cAMP-related syndrome of arrhythmias, vasoplegia, and distributive hypokalaemia due to increased Na-K ATPase activity through β2 receptor stimulation, with possible rebound hyperkalaemia later, because of the reversal of the direction of the potassium flux and rapid plasma enrichment from the intracellular space [19–21]. Effects include central nervous system (CNS) and peripheral β1 and β2 receptor stimulation due to the release of catecholamines and accumulation of the second messenger cAMP [7, 9, 22]. Caffeine can increase the production of nitric oxide in vascular smooth muscle cells (mediated via cAMP), contributing to vasodilation [23], while it also inhibits the intracellular receptor adenylate cyclase [19].

Toxicity

Caffeine has a wide therapeutic window and is considered safe if consumed at lower doses (≤400 mg/day in healthy non-pregnant adults [6]) but can cause toxicities, such as tremor, agitation, tachycardia, and nausea/vomiting at higher doses. However, tolerance develops within a few days of consumption, thus adverse effects, such as anxiety and insomnia, are much more likely among non-tolerant consumers compared to regular caffeine users [24]. Although coffee can acutely increase sympathetic activation and blood pressure in non-regular consumers [25], the effects are less evident in regular drinkers and there is currently no evidence that normal doses are associated with an increased risk of arrhythmia [26, 27]. However, case reports of coronary artery vasospasm and myocardial infarction following an acute overdose of caffeine or caffeinated energy drinks can be found [28, 29]. Other serious symptoms seen during caffeine overdose include seizures, hypotension due to peripheral vasodilation, electrolyte disturbances (most importantly hypokalaemia), and cardiac arrhythmias [6, 7, 9]. The estimated lethal dose is approximately 150–200 mg/kg based on case reports [7, 9] and serum concentrations >80 mg/l are associated with lethal outcomes in acute toxicity, although surviving cases with higher concentrations, as well as rare fatal cases at lower concentrations with comorbidities and co-used substances as possible confounding factors, have been reported [6, 7, 9]. Treatment in cases of toxicity is mainly supportive, for example, antiemetics for nausea, intravenous fluids for hypotension, benzodiazepines in cases of seizures and agitation, and beta-blockers in cases of tachyarrhythmias or refractory hypotension to counteract the β2 receptor-mediated vasodilation and improve tachycardia-associated decreased output [6, 7, 9]. Activated charcoal can be administered for decontamination and haemodialysis can be considered in severe cases [7, 9, 30]. The use of intralipid infusion has been described in a case report of near-fatal overdose [19]. Chronic toxicity in the case of regular consumption of high doses (typically 1–1.5 g/day) may present as a combination of symptoms, such as irritability, anxiety, palpitations, and muscle twitching, also referred to as "caffeinism" [6, 7, 9]. Chronic high intake of coffee might be associated with lower bone density among older women [31, 32]. The abrupt termination of chronic consumption can cause withdrawal symptoms, such as headache, drowsiness, irritability and depression, starting hours after the last consumption, peaking after 1–2 days, and lasting approximately one week [7, 33]. After heavy consumption during pregnancy, neonatal withdrawal syndrome has been described [34, 35]. Caffeine does not appear to be teratogenic when consumed in normal amounts; however, the limitations of such analyses include the diffi-

culty of performing standardised studies, as well as possible confounding factors for some effects [17]. In children, caffeine can acutely enhance performance, but with regular use, it can result in withdrawal symptoms that could impair cognitive function during school [36, 37].

Interactions

In addition to genetic polymorphisms that can affect the metabolic rate of caffeine (differences in clearance between "slow" and "fast" metabolisers [6]), interactions with other substances can also influence its metabolism. Among others, alcohol, grapefruit juice, some quinolone antibiotics, the antidepressant fluvoxamine, the H2 receptor antagonist cimetidine, and oestrogens inhibit caffeine's metabolism leading to longer elimination half-life, while drugs such as rifampicin, phenytoin or omeprazole and tobacco smoke induce its metabolism, thus resulting in shorter elimination half-life [6, 7, 9, 24, 38]. Smoking cessation and thus termination of this induction can lead to higher serum concentrations due to reduced clearance [7, 39]. Concurrent consumption of coffee can lead to decreased absorption of L-thyroxine, alendronate, iron, and zinc [38, 40, 41]. In addition to pharmacokinetic interactions, pharmacodynamic interactions between caffeine and other substances are also possible, such as additive effects and potential toxicity in combination with theophylline [42].

Therapeutic use

Current medical indications include the treatment of apnoea in premature infants and its use as an analgesic adjuvant [7, 13, 43]. In the context of apnoea in prematurity, caffeine is administered intravenously with an initial loading dose, followed by a maintenance dose. Although the mechanism of ventilation improvement in this setting is not fully understood, caffeine's effects include antagonism of the inhibiting respiratory effects of adenosine [43]. As an analgesic adjuvant, caffeine is usually used for the treatment of headaches or migraine in combination with analgesics such as paracetamol (acetaminophen) or aspirin [44]. Caffeine is also used for cognitive enhancement [5, 45, 46].

Several studies investigating non-genetic factors related to the development of Parkinson's disease have shown a reduced risk in association with coffee consumption [47, 48], suggesting a potential neuroprotective effect of caffeine [49, 50]. However, exact data on coffee consumption are often not recorded or considered when designing and conducting large clinical trials and are also difficult to monitor [50, 51]. Furthermore, there are indications that these findings differ between men and women, depending on the use of postmenopausal hormones, with no protective effect or even increased risk associated with the latter [52, 53]. Further reports of potential positive health effects of coffee include a reduced risk of Alzheimer's disease [54], diabetes mellitus type 2 (including with consumption of decaffeinated coffee) [38, 55], and liver cirrhosis [38, 56]. However, similar to studies investigating other potential indications, limitations include possible confounding factors and self-reported consumption [55, 56].

Nicotine

Nicotine is the main driver of tobacco dependence. The *Nicotiana tabacum* plant produces different alkaloids, with the most abundant and major active ingredient being nicotine, which serves the plant as an insecticide [57]. Tobacco leaves are processed for various products, such as cigarettes, cigars, hookah, snuffing tobacco, snus or "heated tobacco" sticks, while extracted and purified nicotine is used for the production of, for example, nicotine replacement products, e-liquids, and nicotine pouches. Although harvesting, extraction and purification are cheaper than the chemical synthesis of nicotine, synthetic nicotine has recently emerged in the nicotine products market [58]. Governing bodies, such as the United States Food and Drug Administration (FDA), initially only had the authority to regulate tobacco-derived nicotine [59]. Manufacturers exploited this by introducing synthetic nicotine into the market, thus evading regulation. While the FDA closed this loophole in 2022 [60], other governing bodies have yet to do so [61]. Importantly, synthetic nicotine may be chemically different from tobacco-derived nicotine. Nicotine can exist as the *(R)* or *(S)* enantiomer; plant-derived nicotine overwhelmingly consists of *(S)*-nicotine (>99%), while synthetic nicotine may be a 50:50 mixture of the two enantiomers [58]. However, stereoselective synthesis of nicotine is possible, and synthetic nicotine products can be almost pure *(S)*-nicotine [62–64].

Pharmacokinetics

An average tobacco cigarette contains about 10–14 mg of nicotine, of which 1–1.5 mg becomes systemically available during smoking [65]. Nicotine is extensively distributed to body tissues (volume of distribution of 2.6 L/kg) and can pass the blood-brain and placental barriers [65]. Genetic influences account for 60–80% of the variability in nicotine metabolism, whereas non-genetic and environmental influences also contribute to the variation [66]. Metabolism is highly dependent on CYP2A6, accounting for ~80% of nicotine's total clearance [67] and mediating the biotransformation of nicotine's major primary metabolite, cotinine. Of the nicotine, 70–80% is transformed to cotinine, whereas 8–10% is excreted unchanged via urine. Cotinine is also a substrate of CYP2A6 and is metabolised to 3'-hydroxycotinine (3'-OH-cotinine), and 33–40% of the total nicotine is excreted as 3'-OH-cotinine in urine [67]. Cotinine clearance is significantly lower, and nicotine clearance tends to be lower in Black people compared to White people [68]. Whites and Latinos exhibit comparable nicotine clearance, whereas Chinese-Americans are reported to have lower clearance [69]. Female sex hormones, specifically oestrogen, accelerate nicotine clearance with higher clearance in women overall, particularly in those using oestrogen-containing contraceptives compared to those who do not, and during pregnancy compared to postpartum [70–72]. Elderly people (>65 years) have a 23% lower nicotine clearance compared with younger adults [73]. Nicotine serum concentrations in smokers tend to be consistent from day to day, as users self-titrate their intake in order to reach desirable levels [74, 75]. However, fast nicotine metabolism is associated with smoking more cigarettes per day and higher dependence, leading to

stronger cravings and lower successful nicotine cessation [76].

Pharmacodynamics

Nicotine's pharmacological effects are mediated through binding to nicotinic acetylcholine (nACh) receptors, which are present in neuromuscular junctions, autonomic ganglia, and the brain [77]. Dependence is largely mediated by neuronal nicotinic acetylcholine receptor activation in the ventral tegmental area and the nucleus accumbens [78]. Nicotine binding leads to a release of dopamine, similar to other drugs that cause dependence [78]. Chronic exposure leads to neuroadaptation, which underlies nicotine dependence and tolerance [79]. Withdrawal symptoms include depression, anxiety, mood disturbances, impatience, difficulty concentrating, insomnia, and restlessness [80]. These symptoms typically start within 1–2 days of stopping nicotine use, peak in the first week and can last up to 3–4 weeks [80]. However, individuals who have quit smoking continue to face a heightened risk of relapse, even after extended periods of abstinence [81]. The effects of *(R)*-nicotine, which is barely present in tobacco, in humans are largely unknown. Research in animals has shown that stereoisomerism of nicotine influences its disposition kinetics [82, 83] and that *(R)*-nicotine has lower potency at nicotine receptors [84].

Toxicity

Green tobacco sickness is a condition commonly found in tobacco harvesters who absorb nicotine through their skin when handling wet tobacco plants, sometimes resulting in acute nicotine intoxication [85]. Traditionally, nicotine was consumed only as part of the tobacco plant. With the emergence of isolated nicotine in products, such as e-cigarettes and oral nicotine pouches, the nicotine concentration is no longer limited to the content in the plant, and more highly concentrated products are available, potentially posing greater risks of acute intoxication. Lethal ingested oral doses of nicotine have been estimated to be 6.5–13 mg/kg body weight [86–88]. However, based on reports of non-fatal cases with much higher doses, these estimates might be too low [87], while tolerance also has an influence. Mild symptoms of intoxication are mainly cholinergic and include nausea, vomiting, diarrhoea, respiratory difficulty, and initial tachycardia, followed by bradycardia as toxicity progresses [85]. Severe intoxication can lead to seizures, hypotension, and respiratory depression, which can be lethal [89]. Children are especially vulnerable and symptoms may occur after ingestion of even 1 mg of nicotine, with the minimum estimated lethal dose being 1 mg/kg body weight [90]. The majority of consultations in poison centres regarding e-liquid exposure concern children. Exposure is mostly unintentional, as children are easily attracted to the appealing flavourants of nicotine products [91, 92].

Interactions

Menthol is commonly added to tobacco or e-liquids as a flavourant for its cooling, soothing and anaesthetic effects, and is also metabolised via CYP2A6 [93]. Smokers of mentholated cigarettes have decreased rates of nicotine metabolism, potentially through enzyme competition [94]. Furthermore, because of its anaesthetic effects, menthol suppresses smoke-related irritation and thus facilitates inhalation and increases nicotine exposure [95]. Known drug interactions that lead to decreased nicotine metabolism include those with methoxsalen, selegiline or tranylcypromine [96]. Tobacco smoke induces the expression of CYP1A1 and CYP1A2, leading to faster metabolism of substances primarily metabolised by these enzymes, e.g. caffeine, haloperidol, propranolol, and oestradiol [97].

Therapeutic use

Nicotine is used as a therapeutic agent in nicotine replacement therapy products, helping smokers to quit by alleviating craving and withdrawal symptoms. Nicotine replacement therapy can be divided into short-acting (e.g. gums, inhalers, mouth or nasal sprays) and long-lasting (patches), and a combination of long- and short-acting nicotine replacement therapy products is more effective in promoting smoking cessation [98]. Nicotine replacement therapy products demonstrate low abuse liability, as they result in lower peak concentrations delivered less rapidly than cigarettes [99]. Addiction to licensed nicotine replacement therapy is rare among never-users of tobacco [100]. However, in smokers who successfully use such products for smoking cessation, sustained use for longer than the recommended treatment duration is common [101, 102]. Other currently approved treatment options for smoking cessation include the partial nicotinic acetylcholine receptor agonist varenicline and the norepinephrine-dopamine reuptake inhibitor bupropion, while the plant alkaloid cytisine, which has a similar mechanism of action to varenicline, is also used in some European countries [102]. Although these therapeutic options exist and most smokers would like to quit, smoking cessation rates remain low [102].

Individuals suffering from mental illnesses, such as schizophrenia, major depression, generalised anxiety, and substance-use disorders, have higher smoking rates and higher nicotine dependence than smokers without mental illnesses [103]. A common explanation for this association is that patients self-medicate their symptoms with nicotine, as the nicotinic acetylcholine receptor is involved in both schizophrenia and addiction, and nicotine can attenuate extrapyramidal and negative symptoms, particularly anhedonia [104]. Nicotine effects also include improved sensory gating, which can ameliorate schizophrenic symptoms [105]. However, the causality of this association is unclear, i.e. whether smoking can also lead to mental illness and whether this association is based on shared risk factors or if the self-medication hypothesis holds true [106].

Exposure to tobacco smoke, smokeless tobacco, and even dietary nicotine intake has been shown to be inversely associated with the risk of Parkinson's disease [107–109]. In a study investigating the incidence of Parkinson's disease in twins, the twins who smoked had a lower incidence than their non-smoking twins [110]. These results point towards a possible protective effect of nicotine. However, several clinical trials investigating the effects of nicotine patches and gums on disease progression have yielded mostly negative results [111–113]. Nicotine has also been suggested to be an enhancer of cognitive performance in patients with

Alzheimer's disease. Studies have reported an inverse relationship between smoking and the latter [114]; however, when controlling for industry affiliation and study design, smoking was found to increase the risk of Alzheimer's disease [115]. While nicotine has been shown to improve the pathology in animal models [116, 117], it has failed to improve the memory of patients in clinical studies [118, 119]. However, positive effects on attention have been observed [119].

Smokers are less affected by ulcerative colitis than non-smokers or former smokers [120]. This association has been largely attributed to the anti-inflammatory properties of nicotine. Nicotine activates the cholinergic anti-inflammatory pathway by binding to a7 nicotinic acetylcholine receptors, which regulate cytokine production through suppression of nuclear factor-kB and inhibition of innate immune responses, limiting potentially hazardous inflammatory responses in the protective and non-toxic range [121]. Animal studies have shown that the activation of the cholinergic pathway can protect against immune-mediated diseases, such as acute lung injury [122], sepsis [123], viral myocarditis [124], acute kidney injury [125] and neuroinflammation [126]. Activation has not been shown to cause immunosuppression, as pro-inflammatory cytokines are reduced from a toxic to a healthy range [121]. Nevertheless, tobacco smoke contains a plethora of pro-inflammatory substances, leading to various lung disorders, such as asthma and chronic obstructive pulmonary disease [127].

Cannabis

Plants of the genus *Cannabis* and its main species *Cannabis sativa* are cultivated for various purposes. While the term "hemp" is used to refer to the undifferentiated cannabis plant material, it has also come to refer to the fibrous plant stem, which has a wide range of industrial uses, including the manufacture of paper and textiles. The use of plant parts as herbal medicines for gastrointestinal, rheumatologic or infectious ailments can be traced back to ancient China, where occasional mind-altering properties of the preparations were noted [128]. In the following centuries, the psychoactive effects of selectively bred species were utilised for ceremonial and recreational purposes [129]. There have been more than 100 cannabinoids isolated from *Cannabis sativa* [130], which are present alongside other chemical compounds, such as terpenes, flavonoids and alkaloids. The most researched cannabinoids are Δ9-tetrahydrocannabinol (THC), the main psychoactive compound, and cannabidiol (CBD). Cannabinol (CBN) is another phytocannabinoid marketed as an over-the-counter sleeping aid, though formal evidence of its efficacy and safety is lacking [131].

Cannabis can be consumed via different routes and the inter-individual variability in pharmacokinetic profiles is extensive [132]. Smoking and vapour inhalation (e.g. via an electronic cigarette or herb vaporiser) are the most common routes for recreational use, although oral intake is increasing [133]. For therapeutic uses of THC, a spray for oromucosal application has been approved in several countries [134]. CBD is consumed by various routes in complementary medicine, including oral, inhalational, topical and sublingual application, and via oral intake for approved indications [135].

Pharmacokinetics

The phytocannabinoids THC, CBD, and CBN are lipophilic compounds with generally poor and highly variable oral bioavailability [136]. Orally absorbed cannabinoids undergo extensive first-pass hepatic and intestinal metabolism. For THC, oral bioavailability has been reported to range from as low as 6% for edible cannabis products up to 20% for standardised extracts and bioavailability can be increased by consumption of a high-fat meal. While the time to reach peak THC concentrations (T_{max}) is approximately 2 hours when taken on an empty stomach, intake with a fatty meal can increase the T_{max} up to 6–7 hours [137]. In contrast, THC is very rapidly absorbed when cannabis products are inhaled (T_{max} 3–10 min) and exhibits a higher bioavailability by this route (10–35%) [136]. The absorption profile of oromucosally applied THC lies between oral or inhalational routes. It is more rapidly absorbed than after oral application, but not as quickly as via inhalation, as some fraction of buccal THC is swallowed and gets absorbed in the same way as orally applied cannabis products [136]. Cannabinoids bind to albumin and lipoproteins and distribute rapidly to well-perfused organs, such as the brain, heart, lungs and liver. The parent compounds and their metabolites also partition to adipose tissue, where they accumulate after chronic use. After inhalation, THC concentrations peak quickly (within 3–10 minutes) and then decline markedly over the next hour due to extensive tissue distribution [138]. After a single dose, an estimated apparent terminal half-life of 22 hours has been reported for THC, and 31 hours for CBD [132, 139]. After chronic use, a markedly prolonged and variable terminal half-life of 5–13 days was described for THC and 2–5 days for CBD, likely because of redistribution from adipose tissue [132, 140]. Accordingly, after cessation of chronic use, THC metabolites can sometimes be detected for several weeks in urine [141]. As lipophilic compounds, cannabinoids readily cross the placental barrier [142] and can be measured in maternal milk [143].

THC and CBD undergo phase 1 metabolism by CYP enzymes and phase 2 metabolism mainly by glucuronidation, and *in vitro* data suggest that cannabinoids may be substrates of drug transporters such as P-glycoprotein (P-gp) [132]. THC is metabolised by CYP2C9, CYP2C19 and CYP3A4 into the psychoactive metabolite 11-OH-THC, which gets further transformed into the inactive form 11-COOH-THC. CBD is primarily a substrate of CYP2C19 and CYP3A4, with minor contributions of CYP1A1, CYP1A2, CYP2C9 and CYP2D6; data on the pharmacologic activity of resulting metabolites are sparse [136]. Polymorphisms in the genes of the aforementioned metabolising enzymes and drug transporters have been linked to pharmacokinetic alterations in a few studies. For instance, poor metabolisers of CYP2C9 tend to have higher THC and lower metabolite exposure [144].

Pharmacodynamics

Cannabinoids – both naturally occurring and synthetic – exert their effects mainly by modulating the endocannabinoid system, which plays pleiotropic roles in maintaining local homeostasis in multiple organs and comprises several receptors (cannabinoid receptors CB1 and CB2 are the most extensively studied), endogenous ligands (endo-

cannabinoids) and corresponding metabolising enzymes. THC is a high-affinity partial agonist at the G-protein-coupled receptors CB1 and CB2. This distinguishes this phytocannabinoid from synthetic cannabinoids, also called synthetic cannabinoid receptor agonists, which are often full agonists with even higher affinity to these receptors, resulting in increased toxicity [145, 146]. CB1 agonism mediates the most extensively studied effects of THC, including increased appetite, reduced spasticity in certain neurologic conditions, and a wide range of neuropsychiatric manifestations [128]. CBD, in contrast, is a low-affinity negative allosteric modulator of CB1 and CB2 and seemingly exerts mostly indirect effects on the endocannabinoid system, for instance, by influencing endocannabinoid transport via fatty acid-binding proteins. Multiple non-cannabinoid receptors (e.g. serotonin receptors, transient receptor potential channels and $GABA_A$ receptors) are hypothesised to contribute to the wide range of purported immunomodulatory, antioxidant, neuroprotective and psychotropic effects of CBD [147]. A shared effect of THC, CBD and CBN is sedation. However, while CBD does not seem to produce impairing psychoactive or significant cardiac effects, THC can produce marked neuropsychiatric symptoms and tachycardia resulting from stimulation of CB1 receptors in the brain and heart, respectively [136]. Genetic variations affecting cannabinoid receptors and other molecular targets of cannabis are associated with pharmacodynamic changes and the risk of developing a cannabis use disorder [144]. However, there is only limited data on the clinical relevance and therapeutic consequences of cannabis pharmacogenomics [144].

Toxicity

In contrast to synthetic cannabinoids, cannabis products are generally considered to be of low acute toxicity [148]. Children and older patients are, however, more at risk of developing severe symptoms after the consumption of cannabis [149, 150]. A lethal dose in humans has not been established, and the risk of death is considered very low in the general population, but might be elevated in specific contexts, such as the presence of cardiac comorbidities or physical trauma occurring during intoxication [151]. Most cannabis-related toxic effects are an extension of CB1 agonism by THC, while health risks associated with CBD are considered negligible [152]. Neuropsychiatric effects, such as euphoria, alterations of perception, psychosis, paranoia and anxiety, are frequently described after the use or abuse of cannabis with high THC content. THC can also cause orthostatic hypotension and precipitate acute cardiovascular events [153]. Cannabis-induced impairments of cognition and judgement, as well as psychomotor deficits, increase the risk of accidents. After inhalation of a typical single dose of THC-containing cannabis, neuropsychiatric symptoms are typically greatest in the first hour and gradually decline over several hours, with significant driving impairment persisting for 5–7 hours. After oral consumption, a markedly delayed onset of effects and a longer-lasting impairment are expected [154]. Tachycardia may additively increase the cardiotoxic risk of other drugs of abuse, such as stimulants. The treatment of acute cannabis intoxication is supportive. Observation in a quiet environment and avoiding unnecessary stimulation is sufficient in most cases; persistent agitation can be treated with benzodiazepines [149].

Chronic cannabis use has been associated with a range of long-term adverse health effects. If marijuana products are consumed by combustion, similar health concerns as those associated with tobacco products have been raised. Cannabis is an addictive substance and cannabis use disorder, as well as cannabis withdrawal syndrome, are well recognised [152]. The Diagnostic and Statistical Manual of Mental Disorders (DSM–5) has defined a cannabis use disorder as a problematic pattern of cannabis use leading to clinically significant impairment or distress, characterised by several criteria reflecting impaired control, psychosocial distress, risky behaviour, and adaptation [155]. A link with other psychiatric disorders is somewhat more controversial. Associations between cannabis consumption and increased risks of schizophrenia, depression and anxiety have been described, but the underlying causal relationship between these observations is still debated [152, 156]. In the context of heavy cannabis use, a cyclic vomiting disorder termed “cannabis hyperemesis syndrome” can occur. This is thought to result from dysregulation of the endocannabinoid system, possibly involving nociceptive pathways via the transient receptor potential vanilloid 1 (TRPV1) receptors. The observation that hot showers and topical capsaicin, which both activate TRPV1, alleviate symptoms in some users, supports this hypothesis, but other mechanisms likely contribute. Some antipsychotics, such as haloperidol or droperidol, are thought to be more effective than more typical antiemetics in the symptomatic management of this disorder; continued abstinence from cannabis products is, however, the only definitive treatment [157].

As the endocannabinoid system is thought to play an important role in brain development and studies suggest detrimental effects of psychoactive cannabinoids on neural connectivity in children, consumption of cannabis is not recommended during pregnancy and lactation [158]. For similar reasons, the consumption of cannabis products by children and adolescents should also be discouraged. Of particular concern for adolescents is the increased incidence of psychiatric disease, especially psychosis, with regular use of high-potency THC products [159–161].

Interactions

Data on interactions between cannabinoids and pharmaceuticals are sparse and consist primarily of *in vitro* studies, case reports, and theoretical considerations, with very few clinical trials available to reliably assess the clinical relevance [162]. Similar to tobacco, compounds in cannabis smoke induce CYP1A1 and CYP1A2, and the combined use of tobacco and cannabis products produces an additive inductive effect. Regular inhalation of cannabis smoke can lead, among others, to reduced exposure to the antipsychotics clozapine, olanzapine, and chlorpromazine, some antidepressants, such as duloxetine and agomelatine, and the methylxanthines caffeine and theophylline [96]. There are several reports of an increase in the anticoagulant effect of warfarin in combination with cannabis use, which is thought to be mediated by inhibition of CYP2C9 [163–165]. Cannabis consumption is associated with an increase in tacrolimus levels, possibly because of inhibi-

tion of P-glycoprotein and/or CYP3A4 by cannabinoids [162]. The latter mechanism was also proposed as a possible explanation for increased buprenorphine concentrations noted in consumers of cannabis in an observational study [166]. Several clinical trials reported an increase in clobazam levels when the benzodiazepine was combined with CBD, possibly due to CYP2C19 inhibition by the cannabinoid [162]. Conversely, the potent CYP3A4 inhibitor ketoconazole has been shown to increase cannabinoid exposure, while the CYP-inductor rifampicin had the opposite effect [167].

Therapeutic use

While the non-prescription use of phytocannabinoids is widespread and encompasses the recreational use of cannabis (with a varying legal landscape even within the same country, e.g. the US) and the use of CBD products as herbal supplements (for example, self-medication as a sleep aid or management of pain and anxiety), there are only a few approved medical indications for cannabinoids, with regional variations. For instance, in several European countries, a THC-containing cannabis mouth spray can be prescribed to relieve refractory spasticity in multiple sclerosis patients, whereas in the US, the THC/Δ^9-THC analogues nabilone and dronabinol are approved for chemotherapy-induced nausea and vomiting resistant to conventional antiemetics, with dronabinol being additionally indicated for anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS) [152]. CBD is approved for the treatment of severe forms of epilepsy associated with Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis [147]. As an add-on therapy for treatment-resistant epilepsy in general, CBD reduced the occurrence of seizures by 50% or more, with a number needed to treat of 8 [168]. The cannabinoid exhibited a favourable safety profile, characterised mainly by mild to moderate adverse events, such as drowsiness, ataxia and diarrhoea. There have been reports of transaminase elevations leading to cessation of CBD therapy and the combination with other antiepileptic drugs, such as valproate, may increase the risk of hepatotoxicity [169].

Cannabinoids, mainly THC and CBD, are being investigated for the treatment of a myriad of other conditions. THC has been proposed as a treatment for chronic pain, glaucoma and some psychiatric diseases, such as Tourette's syndrome and insomnia, but robust evidence of efficacy and safety for most off-label indications is lacking. Cannabis for chronic pain has garnered much interest [2], but it is unclear if the analgesic benefits outweigh the increased risk of adverse effects [170]. Products with a high THC-to-CBD ratio appear to be associated with short-term improvements in pain severity at the cost of frequent occurrences of sedation and dizziness [171]. Similarly, since the evidence of benefit in other off-label indications is generally low quality or lacking, whereas neuropsychiatric adverse effects are well described, doubts about the benefit-risk ratio of cannabis for the treatment of these conditions have been raised [152].

After noting that CBD counteracted some THC-associated psychotic symptoms when co-administered, extensive research has been conducted into the antipsychotic and antianxiety effects of CBD. While preliminary evidence is encouraging, with one study suggesting similar efficacy and superior safety of CBD compared to amisulpride for the treatment of schizophrenia [172], much uncertainty remains about optimal dosing and a place in therapy of this cannabinoid [173]. Other active areas of research are the potential uses of CBD in the treatment of neurodegenerative diseases and inflammatory bowel disease [152].

Psilocybin

Psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine) is a naturally occurring psychedelic agent found in many species of mushrooms of the genus *Psilocybe,* such as *Psilocybe cubensis* and *Psilocybe mexicana* [174, 175]. There has been renewed interest in the use of psilocybin for the treatment of various psychiatric disorders and psychoactive mushrooms have been used for recreational, spiritual and ethnomedical purposes for over 1000 years [174, 175]. Psilocybin and its active metabolite psilocin (4-hydroxy-*N,N*-dimethyltryptamine, 4-HO-DMT) were first isolated, identified and synthesised in the late 1950s by the Swiss chemist Albert Hofmann [176]. In the 1960s, tablets containing 2 mg psilocybin were distributed by Sandoz Pharmaceuticals under the trade name Indocybin™ and were used as an adjunct to psychotherapy and for psychiatric research. However, the increasing popularity of recreational psychedelic use led to its classification as a Schedule I drug in 1970 in the US, and human research with psilocybin came to a halt until the 1990s. Nevertheless, recreational use of psilocybin-containing products has continued and has increased lately in the US [177, 178].

Psilocybin is typically used orally. For ethnomedical or recreational use, usually fresh or dried mushrooms or truffles (sclerotia) are consumed, but psilocybin can also be chemically synthesised and used as a pure substance as in the clinical trials investigating its therapeutic potential [174–176, 179]. Self-reports indicate that for recreational use, dosages ranging from 10 to 50 g of fresh mushrooms or 1 to 5 g of dried mushrooms are ingested [180] with an average psilocybin content of around 10 mg psilocybin (1%) per gram of dried *Psilocybe cubensis* [181]. There is considerable variability in psilocybin and psilocin content between different mushroom species and also within the same species according to the season, as well as the origin or size of the mushroom [180, 182–185]. Furthermore, *psilocybe* mushrooms, in addition to psychoactive compounds, including psilocybin and psilocin, may also contain baeocystin (4-phosphoryloxy-*N*-methyltryptamine) and norbaeocystin (4-phosphoryloxytryptamine) along with other potential psychoactive constituents (summarised in [179, 186]).

Pharmacokinetics

Psilocybin is a prodrug that is rapidly dephosphorylated to its active metabolite psilocin after oral ingestion by intestinal alkaline phosphates and nonspecific esterases [187–192]. Psilocin is subject to extensive metabolism, and around 80% is metabolised via glucuronidation through UDP-glucuronosyltransferase (UGT)1A9 in the liver and UGT1A10 in the small intestine, resulting in the formation of the inactive psilocin-O-glucuronide [186, 190, 193–196]. Additionally, psilocin undergoes deamina-

tion and oxidation by liver aldehyde dehydrogenase and monoamine oxidase (MAO), leading to the formation of the inactive 4-hydroxyindole-3-acetic acid (4-HIAA) [194, 197]. In a study of healthy volunteers receiving 1 mg psilocybin base intravenously and 0.224 mg/kg psilocybin base orally, the estimated mean systemic availability of psilocin was 52.7 ± 20% of the oral psilocybin dose [187]. Administration of oral psilocybin displays dose-proportional changes in plasma concentrations of unconjugated psilocin, psilocin glucuronide, and 4-HIAA with dose-dependent urinary recovery [190]. Following oral psilocybin administration, psilocin is detected in plasma within 20–40 minutes, and maximal plasma psilocin concentrations are reached within 2–3 hours [190, 197–199]. Psilocin and its metabolites demonstrate first-order elimination kinetics with a plasma half-life of psilocin ranging between 1.5 and 3 hours after oral ingestion [187, 190, 194, 198, 199]. Approximately 55% of an orally administered psilocybin dose is excreted through the kidneys within 24 hours in the form of 4-HIAA, unconjugated psilocin, or psilocin-O-glucuronide [190]. Only a small amount of psilocin is eliminated unchanged in the urine (1.5–3.5%) [190, 194, 198] indicating that no dose adjustment is needed in patients with mild to moderate renal impairment. In studies with healthy volunteers, plasma concentration changes of psilocin over time closely mirrored subjective effect-time curves within subjects, and no acute tolerance was observed [190]. CYP2D6 does not appear to significantly contribute to the metabolism of psilocin [196]; however, only limited pharmacogenetic information is available.

Pharmacodynamics

The subjective effects of psilocybin are primarily mediated by agonism at the serotonin 5-hydroxytryptamine-2A (5-HT_{2A}) receptor [200]. However, psilocin also binds to other serotonergic receptors (5-HT_{1A}, 5-HT_{1D} and 5-HT_{2C}) and acts as a serotonin transporter (SERT) inhibitor, but unlike lysergic acid diethylamide (LSD), dopamine receptors seem to be less or not involved [186, 192, 197, 201]. The threshold dose for subjective effects is 2 (range: 1–5) mg [197, 202, 203]. Oral doses of 15–25 mg psilocybin can be considered intermediate doses, whereas oral doses of 30–40 mg psilocybin are considered high [190, 197, 199, 203, 204]. Subjective and autonomic effects are dose-dependent, and psilocybin at moderate to high doses induces pronounced alterations of waking consciousness, including altered perception of time and space, visual (pseudo)hallucinations (recognised by the person experiencing it as being subjective and unreal, in contrast to “true” hallucinations, which are considered “real” by the person), audio-visual synaesthesia, experiences of unity, mostly positively experienced derealisation and depersonalisation phenomena, and mystical-type experiences but also ego dissolution, and anxiety [187, 197, 199, 202–204]. Typically, effects following oral ingestion of psilocybin start after around 20–50 minutes and peak subjective effects are reached around 1.5–2 hours after ingestion [190, 199, 202, 204], aligning with the peak maximal observed psilocin plasma concentrations [190]. The effect intensity and duration are dose-dependent (5.5–6.5 hours for moderate to high doses of oral psilocybin) [190, 197, 199, 202, 204].

Toxicity

Overall, psilocybin exhibits a relatively favourable somatic safety profile [197, 199, 204–206] and shows low abuse liability and no dependence syndrome [207]. For rodents, an LD_{50} of 280–285 mg/kg psilocybin was reported [208]. Psilocybin produces dose-dependent but moderate and transient increases in blood pressure, heart rate and body temperature and increases pupil size [199, 202, 204, 206, 209]. Very high doses may increase the QT interval, in particular when combined with drugs prolonging the QT time, such as some antidepressants [210, 211]. However, no effects by electrocardiogram were found in a clinical study using doses in the range of 45–315 µg/kg body weight over 24 hours of continuous recording [202], and one clinical study did not find significant QTc interval prolongation during the peak response to 25 mg psilocybin in healthy volunteers [210]. Chronic administration (“microdosing”, i.e. the practice of ingesting sub-threshold doses over several weeks with the aim of achieving potential therapeutic benefits without hallucinogenic or cognitive impairment effects) of psilocybin over a prolonged time (months) may theoretically increase the risk of cardiac valve thickening via 5-HT_{2B} receptor stimulation [212, 213]. Frequently reported side effects, also occurring more frequently at higher dosages, include fatigue, lack of concentration and energy, nausea, headache, inner tension, impaired balance, loss of appetite, and dry mouth [199, 204, 209]. Safety concerns relate to psychological rather than physiological risks [205, 209]. Psilocybin use poses a risk of psychological distress, including fear, anxiety, paranoia and dysphoria, and is, in rare cases, associated with psychosis and hallucinogen persisting perception disorder (HPPD), while fatal accidents and suicide have infrequently been described [179, 180, 205, 214, 215]. Although treatment is supportive, it has been repeatedly shown that pretreatment with the 5-HT_{2A} receptor antagonist ketanserin blocks the effects of psilocybin [200, 216–218] and ketanserin was able to reverse the effects induced by LSD [219]. In mice, no evidence of mutagenicity was observed [220]. In rodents, psilocin has been shown to cross the placental barrier [221], but there are no human reports or data on outcomes following psilocybin use during pregnancy.

Interactions

Previous reports imply potential pharmacodynamic interactions with psilocybin and various antidepressants or mood stabilisers, mainly drugs that affect serotonergic neurotransmission (summarised in [222–224]). However, few data from controlled clinical trials are available. Case reports and non-controlled studies have indicated a generally decreased subjective effect of psychedelics in people undergoing chronic treatment with serotonin reuptake inhibitors (SSRIs) and MAO inhibitors [225–229], whereas an increased subjective and physical response has been reported with chronic use of tricyclic antidepressants or lithium [227]. However, a recent double-blind, placebo-controlled crossover trial in healthy participants did not observe any effect of a 2-week pretreatment with the SSRI escitalopram on the psilocybin-induced positive mood or mind-altering effects but rather a decrease in adverse drug effects, including anxiety [210]. Pretreatment with escitalopram decreased the psilocybin-induced increase in

blood pressure, and no additional increase in body temperature was noted, suggesting no additional serotonergic toxicity [210]. A recent clinical trial evaluating psilocybin in patients suffering from treatment-resistant depression with ongoing SSRI treatment (mean ± SD duration 14.7 ± 13.2 months) also showed good treatment results, and overall, the combination was well tolerated [3].

In controlled clinical trials, pretreatment with the 5-HT_{2A} antagonist ketanserin decreases the effects of psilocybin in a dose-dependent manner [200, 216–218]. Similarly, other drugs acting as 5-HT_{2A} antagonists, including the antipsychotics risperidone and chlorpromazine, which both also act as antagonists at the dopamine D2 receptor, significantly attenuated various facets of psilocybin-induced alterations of consciousness in clinical studies [200, 230]. Interestingly, pretreatment with the dopamine D2 receptor antagonist haloperidol decreased positively experienced derealisation and depersonalisation phenomena but increased anxious ego dissolution, suggesting that classic neuroleptics might enhance some psilocybin-induced psychotomimetic symptoms [200]. Additionally, ongoing treatment with a 5-HT_{1A} antagonist might also decrease psilocybin-induced effects, including perceptual alteration, as has been observed following pretreatment with buspirone [231]. Anecdotal data suggest an increased risk of seizures when psychedelics including psilocybin are used with lithium, but not when co-administered with lamotrigine [222].

Therapeutic use

The use of psilocybin is currently being investigated in the treatment of several psychiatric disorders including depression (e.g. [3, 232]), (existential) anxiety (e.g. [4, 233, 234]), anorexia nervosa [235], posttraumatic stress disorder (PTSD) (e.g. [236]), and substance-use disorder (e.g. [237, 238]) but also in the treatment of some neurological disorders, including migraine and cluster headaches [239, 240]. Due to promising preliminary results, psilocybin was granted a breakthrough therapy designation by the FDA for treatment-resistant depression in 2018 and major depressive disorder in 2019 [241].

Conclusions

While the therapeutic potential of caffeine, nicotine, cannabis, and psilocybin is not yet fully recognised, ongoing research is exploring potential new applications. Each substance exhibits a generally favourable safety profile, and overdose lethality is low. However, the neuropsychiatric risks associated with the consumption of cannabis and psilocybin should be taken into consideration, as well as the detrimental health effects of smoke exposure and dependence liability related to nicotine use, to facilitate a balanced understanding of both benefits and risks.

Financial disclosure
This study received no funding.

Potential competing interests
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. *EL* reports academic institution research support for the investigation of the pharmacology and toxicology of e-cigarettes. *NLB* received consulting fees from Achieve Life Sciences and Qnovia, companies that are developing new smoking cessation medications, and has been a paid expert witness in litigation against tobacco companies. All authors declare that they have no conflict of interest in relation to the content of this work.

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