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Review Article

Plant-Derived Psychoactive Drugs: Mechanisms, Addiction, and Health Consequences

Asad Abbas[1], Hussain Ahmed[1], Syed Mohammad Usman[2], Haadia Surtaj[3], Aisha Naeem[4], Muhammad Jawad Khan[1]*

[1]Department of Biosciences, COMSATS University Islamabad, Islamabad, Pakistan
[2]Department of Biochemistry, McMaster University, Hamilton, ON, Canada
[3]Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada
[4]College of Health Sciences, Qatar University, Doha, Qatar
***Correspondence:** jawadkhan@comsats.edu.pk

Abstract

Plant-derived substances such as cocaine and nicotine are widely abused drugs with diverse pharmacological effects, including psychedelic, stimulant, hypnotic, euphoric, and anticholinergic actions. Each plant source confers distinct characteristics that generate both beneficial and harmful outcomes, primarily affecting the brain but also influencing multiple organ systems. Chronic use often results in addiction due to alterations in neural pathways, with detrimental effects on vital organs such as the heart, lungs, kidneys, and muscles. The impact of these substances depends on the drug type, target organ, and mode of administration. Genetic predisposition and stress substantially influence vulnerability to addiction. Withdrawal symptoms emerge upon cessation as a result of physiological dependence. Addiction not only induces behavioral and neurobiological changes but also appears to accelerate biological aging, reflected in telomere attrition aggravated by oxidative stress. This article provides a comprehensive overview of drug addiction and its consequences for individuals and society. It examines psychoactive substances including cannabis, cocaine, morphine, and nicotine, highlighting their mechanisms of action, physiological effects, and implications for aging. These substances act on specific brain receptors, initially eliciting desired effects but ultimately promoting addiction through receptor desensitization and altered neural function. Addiction arises from the complex interplay of genetics, environment, and substance exposure. Addressing this challenge requires integrated strategies encompassing prevention, effective therapies, and strong support systems.

Keywords: Plant-oriented drugs, psychoactive effects, human wellbeing, aging, addictive substances

1. Introduction

Drug addiction is a multifaceted condition shaped by the interaction of biological, psychological, and social factors that influence its onset, progression, and consequences for individuals and societies. Hallmark features include compulsive substance use, impaired control, and negative emotional states during withdrawal (Ruisoto and Contador 2019). Frequently regarded as a personality disorder, drug abuse is a global epidemic shaped by environmental, physiological, and genetic factors (Saah 2005). Many plants naturally contain compounds capable of altering mood, inducing euphoria, and fostering dependence, with evidence of their recreational use by ancient civilizations for thousands of years. Throughout history, such plant-derived substances have also been employed to relax the mind and enhance well-being (Nguyen 2018).

Psychoactive substances act primarily on the central nervous system (CNS) by selectively binding to specific brain receptors, thereby eliciting their characteristic effects (Dinis-Oliveira 2022). However, prolonged and excessive use reduces receptor availability, weakening the brain's response to natural stimuli. As a result, dopamine signaling becomes blunted, driving individuals to consume increasingly larger amounts of the substance to achieve a sense of pleasure or normalcy, ultimately reinforcing addiction (Merikangas and McClair 2012). Upon cessation, individuals often experience withdrawal symptoms such as distress, anxiety, excessive sweating, and tremors.

Multiple risk factors contribute to the development of drug addiction, encompassing social, biological, and psychological dimensions that collectively increase an individual's susceptibility. Each operates at different levels and exerts distinct influences. Among social determinants, parental substance abuse has been identified as one of the most significant predictors of vulnerability to drug misuse (Zaman et al. 2015). Broader community contexts, including school and workplace environments, peer interactions, religious practices, and media exposure, further shape risk. Biological factors also play a critical role. Specific genetic variants may predispose individuals to addiction, while mutations affecting protein function can alter brain circuits, influencing initial responses to drug use and subsequent neuroadaptive changes with repeated exposure (Nwokike et al. 2021). Psychological factors, such as stress and anxiety, compound vulnerability by intensifying dependence. Addictive substances simultaneously activate the brain's reward circuitry and stress pathways, thereby heightening sensitivity to continued use (Sinha 2005). Extensive research highlights the impact of addictive substances not only on behavior but also on biological aging. Mechanisms include telomere attrition, oxidative stress, and altered brain function. Telomeres typically shorten by 20 - 40 base pairs annually; however, factors such as smoking and elevated oxidative stress accelerate this decline, leading to significantly reduced telomere length (Vakonaki et al. 2019). Table 1 summarizes the details of plant-derived psychoactive drugs, including their sources, active compounds, receptor targets, modes of action, target organs, and effects on telomere length.

This article provides a comprehensive overview of plant-derived psychoactive drugs, focusing on their mechanisms of action, addictive potential, and associated health consequences. It examines various psychoactive substances, including cannabis, cocaine, morphine, nicotine, and caffeine, highlighting their mechanisms of action, physiological consequences, and potential implications for the aging process. These substances exert their effects by interacting with specific brain receptors, initially producing desirable outcomes but ultimately driving addiction through receptor desensitization and altered neural function. Figure 1 illustrates the plant-derived drugs and their short-term and long-term effects on human organs. By exploring these complex interactions, the article underscores the multifaceted nature of drug addiction and its profound biological and societal impact. Although the neurobiological pathophysiology of addiction has been extensively reviewed elsewhere, the present article adopts a focused narrative approach, emphasizing plant-derived psychoactive drugs, their primary molecular targets, addictive potential, and associated health consequences, with the aim of providing integrative overview that is relevant to understand substance effect rather than in-depth mechanistic analysis of the addiction circuitry.

Table 1: Details of plant-derived psychoactive drugs

Name	Plant Source	Active Compound	Receptors	Mode of Action	Target Organs	References
Cannabis	*Cannabis sativa*	THC	CB1, CB2	Stimulation of receptors within the endocannabinoid system	Nerve cells, Immune cells	(Reece and Hulse 2022, Vakonaki et al. 2019)
Cocaine	*Erythroxylum coca*	HCl salt, sulfate and the nitrate salts are occasionally seen	NMDA and the D1 dopamine receptor	Prevents dopamine reuptake by binding to the dopamine transporter, leading to an increased dopamine concentration in synapse, intensifying signals.	The medial area of olfactory tubercle or The ventromedial shell of nucleus accumbens, prefrontal cortex	(Levandowski et al. 2016, Tyrka et al. 2016)
Morphine	*Papaver somniferum*	Morphine, 6 monoacetyl-morphine	μ, δ, κ opioid receptors	One dose can affect multiple molecular processes that take place inside the cell.	Thalamus, cortex, olfactory bulb, hypothalamus, amygdala, and peripheral tissues	(Darvishi and Saadat 2022, Perekopskiy and Kiyatkin 2019)
Nicotine	*Nicotiana tabacum*	Cotinine	N1 (peripheral or muscle) and N2 (neuronal)	Restricts the transmission of nerve impulses, particularly those in eyes, nose, and in the throat mucous membranes.	Hippocampus, cerebellum, thalamus, basal forebrain, and brainstem, and blood vessels	(Chaiton et al. 2016, Liu et al. 2020)
Caffeine	*Coffea arabica*	Methylxanthine	Adenosine receptors	Antagonist of adenosine A_1, A_{2A}, and A_{2B} receptors	Stimulates medullary, vagal, vasomotor, promoting vasoconstriction	(Lazarus et al. 2011, Tao et al. 2021)

2. Role of Cannabis

Plants of the *Cannabis* genus produce a distinct class of compounds known as phytocannabinoids, with approximately 568 unique molecules identified to date. Among these, Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol are the most notable for their psychoactive properties (Lewis et al. 2017). Cannabis is the most widely used illicit drug worldwide, with lifetime prevalence reported at ~46% among adults in the United States (U.S.), 35% in Australia, and 26% in Europe (Boumparis et al. 2019). Globally, about 3.8% of individuals aged 15 - 64 use cannabis, though prevalence in Asia is lower at around 2% (Adinoff and Cooper 2019; Areesantichai et al. 2020). In the U.S., where recreational and medical use is legalized, adolescent marijuana consumption has risen markedly over recent decades (Nguyen 2018).

Cannabis can be consumed through smoking, vaporization, or ingestion, with the route of administration influencing the onset, intensity, and systemic effects of psychoactivity (Borodovsky et al. 2016). Two primary cannabinoid receptors, CB1 and CB2, are G protein-coupled receptors central to cannabis pharmacology (Shahbazi et al. 2020). CB1

receptors are abundant in brain regions such as the cerebellum, hypothalamus, basal ganglia, hippocampus, and basolateral amygdala, which regulate motor coordination, memory, appetite, and emotional responses (Sexton et al. 2019). Endocannabinoids, including anandamide and 2-arachidonylglycerol, act as endogenous ligands that modulate CB1 receptor activity (Shahbazi et al. 2020). Δ^9-THC binds strongly to CB1 receptors, producing cerebral effects but potentially disrupting prefrontal cortical systems critical for working memory and attention (Lupica and Hoffman 2018). In contrast, CB2 receptors are primarily expressed in immune cells, where they are thought to regulate cytokine release and immune responses, though their precise roles remain less defined (Katchan et al. 2016).

Cannabis use has been associated with a range of psychosocial and physical harms. These include elevated risks of psychosis, anxiety, impaired learning, reduced social functioning, socioeconomic difficulties, panic attacks, and diminished quality of life (Boumparis et al. 2019). Short-term effects encompass impaired judgment, paranoia, poor memory, confusion, coordination deficits, and risky decision-making, while long-term use is linked to addiction, structural and functional brain changes, cognitive decline, educational setbacks, persistent psychiatric disorders, accidents, injuries, and increased suicide risk (Simpson and Magid 2016; Bahji et al. 2020). At the cellular level, cannabis inhibits telomerase activity, an enzyme critical for maintaining telomere length during cell division, thereby contributing to accelerated biological aging (Reece and Hulse 2022).

Beyond its psychoactive and addictive properties, cannabis exerts diverse pharmacological effects on human health and well-being. Acute use may produce relaxation, altered sensory perception, analgesia, and appetite stimulation; however, it can also impair attention, reaction time, and executive function. Chronic use has been associated with deficits in learning and memory, reduced motivation, sleep disturbances, and increased risk of anxiety and depressive symptoms. Respiratory complications, impaired driving performance, and reduced occupational functioning further illustrate its broader impact on daily well-being (Borrego-Ruiz et al. 2025).

3. Role of Cocaine

Cocaine is the second most commonly used illicit drug in Europe after cannabis (Spronk et al. 2013). Derived from the coca plant *Erythroxylum coca* native to South America, cocaine is one of several alkaloid compounds, but it is the principal psychoactive constituent (Biondich and Joslin 2016). Cocaine exists in two main forms: freebase and hydrochloride (HCl) salt. Freebase cocaine, commonly referred to as "crack," is insoluble in water and typically produced by heating cocaine HCl with baking soda and water. In contrast, the hydrochloride salt is water-soluble and can be readily snorted or injected (Roque et al. 2022). Cocaine use is widespread globally, particularly among young adults in urban settings. It is highly addictive and closely associated with both illicit and, in some contexts, legal drug markets (Akasaki and Ohishi 2020). Routes of administration include ingestion, smoking, intravenous injection, nasal insufflation, and oral application. Its pharmacokinetics vary by administration route, but once absorbed, cocaine is primarily metabolized in the liver by cholinesterases into benzoylecgonine and ecgonine methyl ester. These polar metabolites are excreted in urine and can be detected for 24 - 36 hours after use (Kim and Park 2019).

Cocaine exerts its effects by blocking the reuptake of dopamine, serotonin, and noradrenaline in the CNS, thereby elevating the

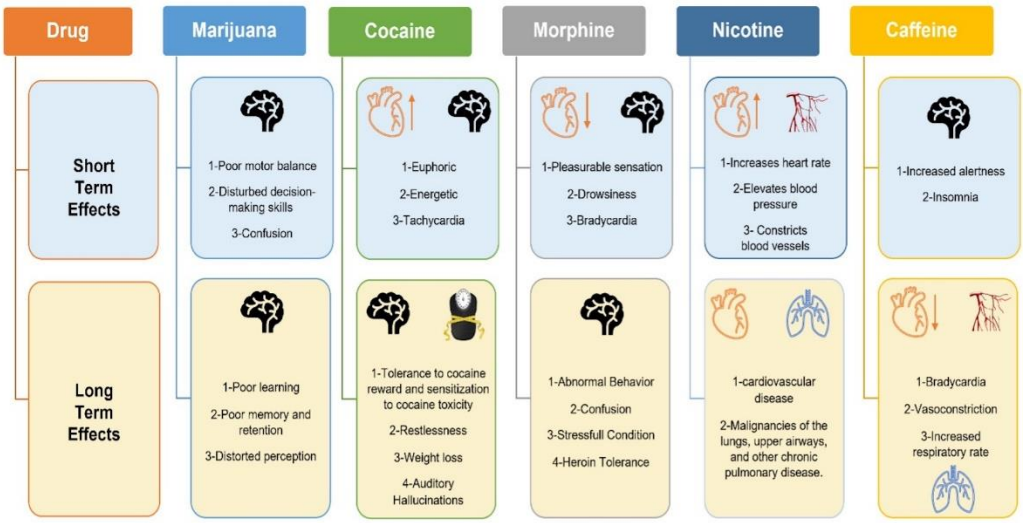

Figure 1: Plant-based drugs and their short-term and long-term effects on body organs.

synaptic concentrations of these neurotransmitters. Additionally, it directly affects mucosal membranes, inhibiting nerve conduction, and enhances sympathetic activity by preventing noradrenaline reuptake, which potentiates catecholamine effects (Grzybowski 2008). Chronic or abusive cocaine use is associated with severe social, psychological, and medical consequences, including cardiac damage, anxiety disorders, aggression, and criminal behavior (Spronk et al. 2013). Physiologically, long-term use contributes to peripheral vascular disease, tachycardia, hypertension, chest pain, hemorrhagic and ischemic strokes, chronic heart failure, and renal dysfunction (Akasaki and Ohishi 2020).

At the molecular and cellular level, cocaine use has been linked to elevated peripheral inflammatory mediators and reductions in grey matter volume, both of which parallel processes observed in aging and age-related diseases. Co-use of cocaine with other substances such as alcohol and heroin further accelerates biological aging, increasing risks of immunosenescence and telomere shortening (Levandowski et al. 2016). Moreover, chronic stress, a common comorbidity in cocaine users, also exacerbate the psychiatric symptoms and is independently associated with telomere attrition. This relationship appears mediated by glucocorticoid activation, oxidative stress, and pro-inflammatory cytokines, suggesting a synergistic interaction between drug use, stress exposure, and accelerated cellular aging (Tyrka et al. 2016).

The pharmacological effects of cocaine extend beyond euphoria and addiction to include pronounced cardiovascular and neuropsychiatric consequences. Acute use can result in hypertension, arrhythmias, hyperthermia, agitation, and psychosis, however, chronic use is linked to cognitive impairment, mood disorders, and social dysfunction. These effects substantially diminish quality of life and contribute to increased morbidity and mortality (Grzybowski 2008).

4. Role of Morphine

Morphine is the predominant alkaloid in the opium poppy, followed by thebaine, noscapine, codeine, and papaverine. Among the 110 *Papaver* subspecies, only *P. somniferum* and *P. setigerum* produce narcotic compounds such as codeine

and thebaine. Although *P. setigerum* contains higher papaverine levels, it has less morphine compared to *P. somniferum*. The morphine content in raw opium varies considerably between countries (3 - 30%), although dried poppy capsules generally maintain more stable concentrations (0.2 - 1.0%) (Choe et al. 2012; Tittarelli et al. 2022).

The protein catechol-O-methyltransferase (COMT) modulates dopaminergic pathways and contributes to opioid-induced side effects such as nausea and vomiting. Opioid actions engage multiple signaling cascades and neuronal receptor interactions, including those involving COMT, which converge at the medullary "vomiting center" (Laugsand et al. 2011). Binding of opioids to OPRM1 receptors also disrupts gastrointestinal function, causing constipation through delayed gastric emptying, altered intestinal transit, and impaired motility (Laugsand et al. 2015).

Genetic factors play a significant role in opioid response. Adverse opioid-related outcomes have been linked to 33 genes and 71 single-nucleotide polymorphisms (SNPs): nine are associated with clinical complications (e.g., arrhythmia, length of hospital stay, mortality), 13 with respiratory depression, and 50 with opioid misuse behaviors (Ahmed et al. 2019). Heroin rapidly crosses the blood-brain barrier (BBB) and is metabolized into 6-monoacetylmorphine (6-MAM) before being converted to morphine (Perekopskiy and Kiyatkin 2019). Chronic heroin and morphine use induces oxidative stress, overwhelming antioxidant defenses and leading to telomere shortening. This strong association between opioid use and telomere attrition highlights how addiction accelerates physiological processes of aging and undermines overall health (Darvishi and Saadat 2022). Genetic variation plays a central role in opioid dependence, influencing receptor sensitivity, drug metabolism, adverse outcomes, and misuse behaviors. These shared genetic determinants suggest overlapping biological vulnerabilities across different classes of addictive substances (Wang et al. 2019).

Although morphine is clinically valuable for pain management, non-medical use produces profound effects on human well-being, including sedation, impaired cognitive and motor function, endocrine disturbances, gastrointestinal dysfunction, and increased susceptibility to infections. Long-term misuse often leads to social isolation, reduced occupational performance, and psychological dependence (Dowell et al. 2022).

5. Role of Nicotine

Nicotine, a natural alkaloid present in tobacco, is derived primarily from *Nicotiana tabacum* (large-leaf tobacco) and *Nicotiana rustica* (small-leaf tobacco). Common routes of nicotine administration include smoking, chewing, and inhalation of powdered tobacco, though it is also used in pharmacotherapy for smoking cessation. In response to global tobacco control initiatives, nicotine replacement products such as patches, gums, e-cigarettes, and inhalers have been developed and marketed as alternatives (Piña et al. 2018). Despite these measures, nicotine remains highly addictive, exerting its effects by binding to nicotinic acetylcholine receptors (nAChRs) in the brain and peripheral organs. Cigarette smoke delivers nicotine efficiently by bypassing intestinal and hepatic first-pass metabolism. Within 2 - 8 seconds of inhalation, nicotine crosses the BBB and diffuses into brain tissue. Owing to its relatively long half-life of ~20 hours, nicotine accumulates in the body (Wittenberg et al. 2020). Neuroimaging studies demonstrate that nicotine alters activity in the frontal lobe, thalamus, and visual processing regions, consistent with its influence on corticobasal ganglia-thalamic circuits. Activation of nAChRs triggers the release of

multiple neurotransmitters including dopamine, norepinephrine, serotonin, acetylcholine, γ-aminobutyric acid (GABA), endorphins, and glutamate, producing diverse physiological and psychological effects. Over time, tolerance develops as certain effects diminish. As a sympathomimetic, nicotine promotes catecholamine release, elevating blood pressure and heart rate while inducing vasoconstriction (Benowitz 2009).

Nicotine is metabolized primarily in the liver by the enzyme CYP2A6, yielding cotinine as its major metabolite. Cotinine is widely used as a biomarker of nicotine exposure. Genetic polymorphisms in CYP2A6 lead to interindividual differences in nicotine metabolism, with faster clearance observed in Caucasians than in Asians and Africans. Sex hormones further modulate enzyme activity, contributing to faster metabolism in females (Derefinko et al. 2018; Rao et al. 2018).

Nicotine dependence arises from neuroplastic changes within CNS circuits, particularly the mesolimbic dopamine pathway, following repeated activation of nAChRs (Changeux 2010). Both genetic and environmental factors influence dependence, with heritability estimated at ~50% (Greenbaum and Lerer 2009). Genome-wide association studies (GWAS) have identified SNPs in genes encoding nAChR subunits, notably clusters on chromosomes 8p11 and 15q25 (CHRNA5-CHRNA3-CHRNB4; CHRNB3-CHRNA6) as well as CHRNA4 (Greenbaum and Lerer 2009; Bierut 2011; Hancock et al. 2015). Early studies suggest that multiple nAChR subtypes, with distinct expression patterns and sensitivities, contribute to tobacco addiction (Changeux 2010; Picciotto and Kenny 2013). Beyond elucidating biological mechanisms, genetic and genome-wide association findings in nicotine dependence have important translational implications. Identification of risk variants in nAChR subunits and metabolic enzymes may enable personalized risk assessment, allowing early identification of individuals with heightened vulnerability to nicotine addiction. Furthermore, genetic differences in nicotine metabolism and receptor sensitivity could inform individualized treatment strategies, including optimized dosing of nicotine replacement therapies and selection of pharmacological or behavioral interventions, thereby improving cessation outcomes and reducing relapse. Collectively, these genetic findings underscore that nicotine dependence is strongly influenced by inherited variation in receptor structure and metabolic pathways, a theme that is also evident in opioid addiction and highlights shared genetic contributions to substance dependence (Muenstermann and Clemens 2024).

Nicotine addiction remains a global health burden, responsible for significant morbidity and mortality. Beyond its established role in cancer, smoking contributes to preterm birth, spontaneous abortion, peripheral vascular disease, cardiac events, and stroke. Most smokers attempt to quit repeatedly before achieving long-term abstinence, with an average of ~30 quit attempts reported (Chaiton et al. 2016). Smoking also increases oxidative stress and inflammation, both of which accelerate aging processes. As telomere shortening is strongly associated with oxidative stress and chronic inflammation, smokers often exhibit reduced telomere length, suggesting that nicotine accelerates cellular aging (Liu et al. 2020).

In addition to its addictive potential, nicotine and tobacco use exert extensive pharmacological effects on multiple organ systems. These include impaired pulmonary function, increased cardiovascular risk, reduced immune competence, and adverse reproductive outcomes. Such consequences have major implications for overall health, productivity, and

life expectancy (Dorotheo et al. 2024).

6. Role of Caffeine

Caffeine (1,3,7-trimethylxanthine) is widely consumed through coffee, tea, and soft drinks. As a naturally occurring methylxanthine stimulant, it enhances CNS activity (Lisko et al. 2017). Among psychotropic substances, caffeine is the most widely used worldwide (Lazarus et al. 2011). Natural sources include kola nuts, tea leaves, cocoa beans, coffee beans, and tea bags (Tao et al. 2021). Caffeine is absorbed primarily through the gastrointestinal tract. Following ingestion, up to 99% is absorbed, about 20% in the stomach and the remaining 80% in the small intestine (Willson 2018; dePaula and Farah 2019). Metabolism occurs mainly via the enzyme CYP1A2 (responsible for ~90% of its biotransformation), with minor contributions from monooxygenase, N-acetyltransferase, CYP1A1, CYP2E1, CYP3A4, and CYP2D6 (Burdan 2015).

Caffeine acts as a natural antagonist of adenosine receptors (A1, A2A, A2B), thereby counteracting adenosine's physiological effects. A1 receptors are broadly distributed across cells, while A2A receptors are concentrated in the basal ganglia, arteries, platelets, heart, and CNS. These receptors regulate cardiovascular and neural functions, including coronary blood flow and myocardial oxygen consumption. Adenosine itself is a potent neurotransmitter that modulates the prosencephalon and brainstem, stimulating dopamine and glutamate release (Magkos and Kavouras 2005; Gao and Jacobson 2011). By blocking A2A receptors in the brain, caffeine may enhance alertness and cognitive performance. However, excessive blockade can contribute to adverse effects such as anxiety, insomnia, and restlessness (Lazarus et al. 2011).

Caffeine also stimulates respiration and increases the secretion of renin, epinephrine, and norepinephrine (Burdan 2015), which can support alertness and short-term cardiovascular responses. At the same time, these effects may elevate blood pressure and heart rate in sensitive individuals. Furthermore, caffeine has been reported to induce telomerase reverse transcriptase (TERT) expression at both mRNA and protein levels, potentially maintaining telomere length and delaying cellular senescence. Nevertheless, these protective effects depend on moderate consumption, as excessive intake can negate benefits and contribute to gastrointestinal disturbances, cardiovascular strain, and impaired motor coordination (Saygin et al. 2020; Tao et al. 2021). Overall, moderate caffeine intake is generally well tolerated and may offer cognitive and cellular benefits, but individual responses vary considerably, and excessive intake can adversely affect well-being.

7. Conclusion

Plant-derived psychoactive substances such as cannabis, cocaine, morphine, nicotine, and caffeine exhibit diverse mechanisms of action and health consequences, ranging from short-term neurobehavioral effects to long-term impacts on organ systems and biological aging. Despite differences in their molecular targets, these substances converge on shared pathways that promote dependence, neuroadaptation, and physiological dysregulation. The evidence summarized in this review underscores that addiction is not only a behavioral disorder but also a condition with measurable biological consequences, including oxidative stress and telomere attrition. Across substances such as nicotine and morphine, converging evidence highlights the importance of genetic variation in receptors, metabolic enzymes, and signaling pathways in shaping individual susceptibility to addiction, treatment response, and long-term health outcomes. Incorporating genetic

information into addiction research may facilitate personalized prevention and treatment approaches, particularly for nicotine and opioid dependence, where heritable variation strongly influences susceptibility and therapeutic response. These findings highlight the need for integrative strategies that address genetic susceptibility, environmental exposure, and psychosocial stressors. From a translational perspective, prevention efforts should emphasize education, early identification of at-risk individuals, and regulation of substance availability. Mitigation and treatment strategies, including behavioral therapies, psychosocial support, and substance-specific pharmacological interventions, remain essential for reducing dependence and relapse. Future research aimed at identifying molecular and cellular targets associated with addiction-related aging may further support the development of novel therapeutic and preventive approaches. Although this review highlights associations between plant-derived psychoactive drug use, addiction, and biological aging, so it is important to acknowledge that many reported findings are observational in nature and do not establish direct causality. Potential confounding factors, including chronic stress, socioeconomic conditions, diet, physical activity, sleep patterns, and co-occurring mental health disorders, may independently influence both substance use behaviors and biological outcomes such as oxidative stress and telomere length. Future longitudinal and mechanistic studies that more rigorously control for these variables will be essential to clarify causal pathways, reduce potential confounding, establish temporal relationships and strengthen interpretation of the observed associations.

Conflict of Interest

The authors declare that they have no competing interests.

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NA

Data Availability

All the raw data related to this study are available with the authors.

Authors Contributions

AA and HA conceptualized and organized the study, SMU and HS did the literature search and analysis, AA and HA wrote the initial manuscript, AN and MJK wrote the final manuscript, and supervised the project.

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