



The prevalence, mechanism of action, and toxicity of Nigerian psychoactive plants

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Abstract

Cannabis sativa, *Datura stramonium*, *Nicotiana tabacum*, and *Carica papaya* are plants that naturally grow in Nigeria. They are reportedly rich in neuroactive compounds that are capable of reacting with the nervous system to elicit psychoactive and/or toxic effects that deter predators. However, despite the toxicological potential of these plants, their recreational use is on the rise due to the psychoactivity they proffer and prevalence in Nigeria. The aim of the present study is to evaluate the plants' recreational use, mechanism of actions and toxicities. Relevant published documents on psychoactive plants in Nigeria were obtained from Web of Science between 2002 and 2020. Non-English documents, documents not in Science Citation Index Expanded and Google Scholar were removed while 1186 documents were reviewed. Results showed that the plants are recreationally used in Nigeria with a higher prevalence than the global frequency. They are very addictive and lead to dependence. The plants were also observed to elicit different mechanism of action, though the activation of monoaminergic neurotransmission system was common to all. Regrettably, the plants could be toxic when ingested under non-medical conditions. Conclusively, these plants are addictive with potential toxic effects. Therefore, control of the recreational use of these plants should be revamped and overhauled.

Keywords Psychoactive plants · *Cannabis sativa* · *Datura stramonium* · *Nicotiana tabacum* · *Carica papaya*

Introduction

Psychoactive substance abuse is still a growing global challenge regarding public health and socioeconomic burden (Soremekun et al. 2021). This global problem is reflected in the high prevalence of drug-associated health problems and a lack of adequate data on the pattern of psychoactive substance abuse in the underdeveloped and developing worlds. In contrast, the developed worlds are characterized by difficulty controlling and preventing psychoactive substance abuse (UNODC 2018). Unravelling the extent of substance abuse is complex and challenging for several reasons, which include the varied nature of abused substances, health issues, social spurn that triggers silence, and varying legal undertones around their use throughout the world (Ogundipe et al. 2018).

The studies of the United Nation Office on Drugs and Crime (UNODC) between 2009 and 2018 (UNODC 2018, 2019) have extensively addressed the prevalent use of psychoactive substances in Nigeria. Some other indigenous studies have evaluated psychoactive plants that have previously been identified to contain psychoactive constituents such as *Datura stramonium*, *Nicotiana tabacum*, and other plants with a dearth of data regarding psychoactive components such as dry *Carica papaya*, *Manihot esculenta*, and *Moringa oleifera*, among others (Abdurahman et al. 2019; Dumbili 2020; Dumbili et al. 2021). However, there is still dearth of information regarding the mechanism of action employed by these plants to exert their neuroactivity and neurotoxicity. Furthermore, the studies address the psychoactive plants as a type of psychoactive substances which are plant based, thereby giving the plants a broad perspective while lacking specificity in research.

Therefore, the present study will address the prevalent use of the psychoactive plants, and their mechanism of neuroactivity and neurotoxicity independently. Understanding the mechanisms that underlie these processes will immensely improve the management and approach of therapy for abuse

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and addiction to psychoactive plants, a baseline for health-care practitioners in clinical studies, and a tool to create a new weapon against their recreational use.

Methodology

The present review focused primarily on psychoactive plants in Nigeria, their mechanism of action and toxicity. Therefore, the words “psychoactive plants”, “plant-based psychoactive substances”, “*Cannabis sativa*” (“+Nigeria” “+ mechanism of action” “+ toxicity”), *Datura stramonium* (“+Nigeria” “+ mechanism of action” “+ toxicity”), *Nicotiana tabacum* (“+Nigeria” “+ mechanism of action” “+ toxicity”), *Carica papaya* (“+Nigeria” “+ mechanism of action” “+ toxicity”), *Manihot esculenta* (“+Nigeria” “+ mechanism of action” “+ toxicity”), and *Moringa oleifera* (“+Nigeria” “+ mechanism of action” “+ toxicity”) were searched from Web of Science Core Collection (WoSCC) on the Web of Science (WoS) database between January 2002 and June 2022 according to the procedure described by Palmatier et al. (2018) from August 2021 to June 2022. The years between 2002 and 2022 were selected to cover the two most recent decades and also that 2022 is the succeeding year after the global alteration in Narcotics Law. From a total of 1796 pooled results, documents that were not of research or review types such as paper proceedings, retracted publications, data papers, editorial materials, letter, meeting abstracts, corrections, poetries, art exhibition reviews, news items, and preprints were excluded to arrive at 1374 documents. Documents written in non-English languages were excluded, after which documents not in Science Citation Index Expanded and Google Scholar were removed to arrive at 1202 documents. The 1202 documents were then independently validated by the authors, 16 documents were

further excluded as they did not meet citation criteria while the remaining 1186 documents were saved in for data visualization and analysis in writing the present review (Fig. 1).

Psychoactive substance abuse in Nigeria

According to the Nigerian Drug Use Survey of 2018, the national prevalence of psychoactive substance use in Nigeria was estimated to be 14.4% of the adult population, a value comparatively high compared to the 5.6% global annual prevalence of substance use (UNODC 2018). The estimated age of first use of psychoactive substances in Nigeria was also observed to be as early as 11 to 12 years, a condition that has been associated with a high prevalence of social, physical, and psychiatric comorbidity at later stages of life (Abdurahman et al. 2019). In addition, the World Health Organization (WHO) also estimated in 2012 that more than 13 million adults in Nigeria were active smokers (World Health Organization 2015). A 3:1 gender ratio of psychoactive substance use by men (21.8%) to women (7.0%) was also observed, with a significant percentage of the women even pregnant during the time of use (Lamy and Thibaut 2010; UNODC 2018). The higher prevalence of men engaging in risky acts due to their high testosterone levels and the more significant restrictions imposed on female wards in Nigeria have been implicated as the causes of this gender disparity (Akanni and Adayonfo 2015). The highest prevalence of psychoactive substance use was found to be among those aged 25 to 39 (Fig. 2). At the same time, the southern geopolitical zones of Nigeria were observed to have a higher prevalence (13.8–22.4%) of substance use compared to the northern geopolitical zones (10.0–14.9%) (Fig. 3) (UNODC 2018).

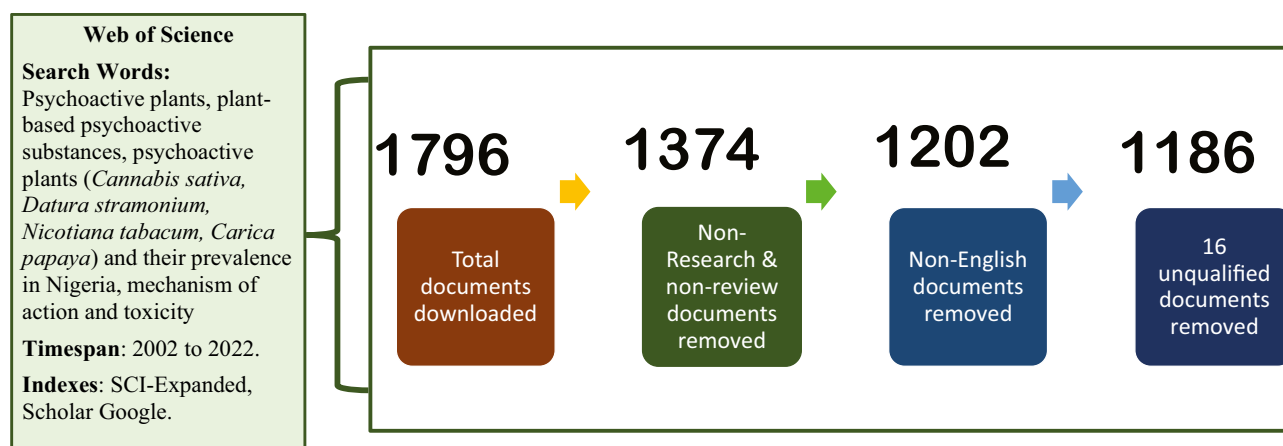
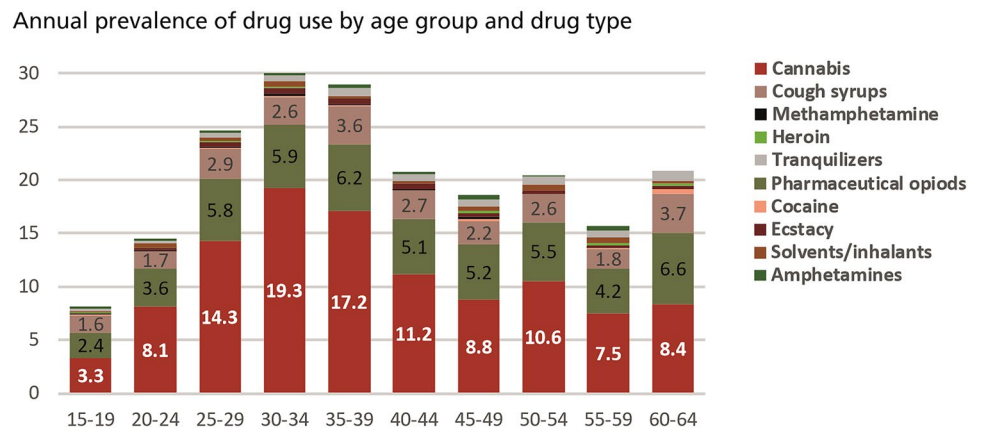


Fig. 1 A systemic flowchart of data collection from Web of Science Core Collection

Fig. 2 Annual prevalence of psychoactive substance use in Nigeria by age and drug type (UNODC 2018)



Furthermore, the survey showed that *Cannabis sativa* is the most abused substance in Nigeria, with a prevalence rate of 10.8% used by the Nigerian adult population, indicating the failure of narcotics prohibition policies to suppress supply and reduce demand for the psychoactive drug plant.

This failure has been severely marked by elevated violence, conflicts, crimes, and even deaths, especially in urban settlements such as Abuja, Kaduna, Kano, Lagos, and Port Harcourt (Klantschnig 2016). In addition to the ineffectiveness of the national narcotics prohibition policy, the prohibition

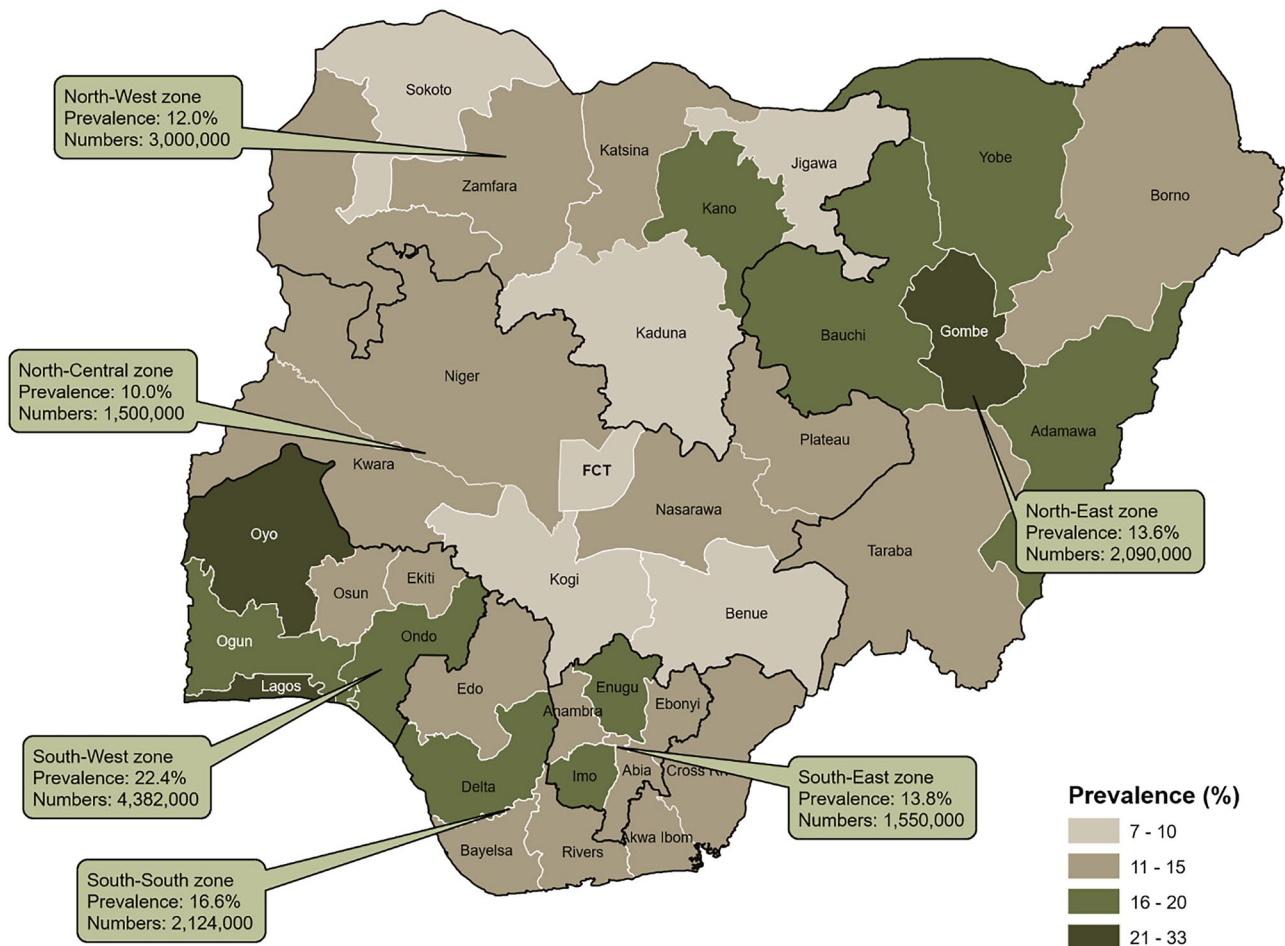


Fig. 3 Prevalence of drug use in Nigeria by geopolitical zones and states, 2017 (UNODC 2018)

of psychoactive substance abuse has been solely pledged to the country's law enforcement agencies instead of addressing it as a full-fledged social matter (Otu 2013). In Nigeria, Opioid and cough syrup were the second and third most abused substances, respectively (UNODC 2018). At the same time, plants such as *Datura stramonium*, *Nicotiana tabacum*, *Carica papaya*, *Manihot esculenta*, and *Moringa oleifera* are also highly abused due to the psychoactive effect they proffer (Dumbili et al. 2021).

The consumption of plant-based psychoactive substances in large quantities during traditional ceremonies and functions in Nigeria further implies that restricting their abuse is ineffective (Abasiubong et al. 2014). Despite the efforts of the Nigerian drug control officers (National Drug Law Enforcement Agency (NDLEA), Nigeria Customs Service (NCS), Nigerian Police Force (NPF), Nigeria Immigration Service (NIS), and Economic and Financial Crimes Commission (EFCC)), illegal cultivation of psychoactive plants is highly prevalent in Nigeria (NDLEA 2015; Alemika 2018). The assessment of armed robbers, militants, kidnappers, rapists, cultists, and terrorists, such as Boko Haram in Nigeria, to these substances and the evil attributed to their use of these substances further illustrates the need to address these community-based psychoactive plants.

However, Nigerian communities have various definitions for the non-medicinal use of psychoactive plants. Some even view it as a regular aspect of their social-life interactions, sacred rituals, and traditional ceremonies (Abasiubong et al. 2014). Some communities even regard it as a disrespectful act and an offence that may attract penalties if products from these psychoactive plants are not provided during traditional functions and ceremonies. According to anthropological literature (Wadley 2016), these products are thought to strengthen communal bonds. Furthermore, *Datura stramonium*, *Nicotiana tabacum*, *Carica papaya*, *Manihot esculenta*, and *Moringa oleifera* are bioavailable plants and not classified as illicit plant-based drugs; they have been labelled non-lethal and safe for recreational use (Corazza et al. 2013). In contrast, the legal status of a psychoactive substance does not always equate to safety (GCDP 2017). The belief that psychoactive plants are the origin of most synthetic psychoactive substances and also proffer similar pharmacological, bodily, and metabolic effects were observed to have motivated Nigerians who could not afford the conventional synthetic psychoactive substances to prefer their use (Cooper et al. 2016; Feng et al. 2017).

In Nigeria, predisposing factors to psychoactive substance use include being born into polygamous, single-parenthood or divorced family settings, poor academic performance and socioeconomic status, pressure from pressure groups, living alone or with friends during teenage years, relaxation, getting high or taking the mind off every day responsibilities' vicissitudes, boosting self-confidence, desire, and

curiosity for adventure (Chikere and Mayowa 2011; Johnson et al. 2017). Willingness to stay awake at night, alleviate depression and anxiety were also discovered to enhance the usage (Amigó 2021; Fasakin et al. 2022a). Maltreatment, assault, and neglect by family or loved ones, as well as imprisonment, were also observed to lead to psychoactive substance use in Nigerian communities (Amdraranda et al. 2009; Atilola et al. 2014). Furthermore, fostering social belonging and bonding as well as enhancing sexual performance and abilities were also identified as the reason for using psychoactive substances (Soussan et al. 2018; Fasakin et al. 2022b).

Only religiosity (UNODC 2018), good parental supervision during adolescence, and engaging the youths in other pleasurable activities other than experimenting with psychoactive plants (Abdurahman et al. 2019; Dumbili 2020), and educating and orienting the Nigerian population about the hazards associated with this substance use (Nwannennaya and Abiodun 2017) have shown significant. Therefore, the present review focuses on one of the effective barriers, educating and orienting the Nigerian population about the mechanisms of action of psychoactive plants and their associated neurodegenerative potential.

Psychoactive plants

Plants naturally manifest arrays of chemicals, of which a percentage of the chemicals have been implicated as being psychoactive in their mode of action. These chemicals are primarily alkaloids and have been observed to act as soporific, stimulatory, sedative, euphoriant, antidepressant, memory enhancers, and psychedelic agents (Jean-Francois 2014; Fasakin et al. 2021). Plants with these characteristics are termed "psychoactive plants." Therefore, the present review defines psychoactive plants as plants with constituents (e.g., alkaloids) that can alter the central nervous and neurotransmitter systems' functioning and induce psychoactivity.

The earliest academic research on psychoactive plants was dated to 1855 when Ernst Freiherr von Bibra's *Die Narkotischen Genussmittel und der Mensch* reviewed seventeen (17) plant narcotics and their probable psychoactive chemistries (Jean-Francois 2014). Due to their mind-altering or hallucinogenic effects, these plants were referred to as "Plants of the gods" in primitive cultures. These cultures customarily considered them sacred and ingested them during religious rites in an attempt to reach and communicate with revered ancestors or gods. Some others also use it as an essential ingredient during healing rites (Faria 2021). The recreational use of psychoactive plants during the Ching Dynasty of China in the nineteenth century resulted in the enactment of laws such as the 1961 Single Convention on Narcotic Drugs, with further reviews of the law during the

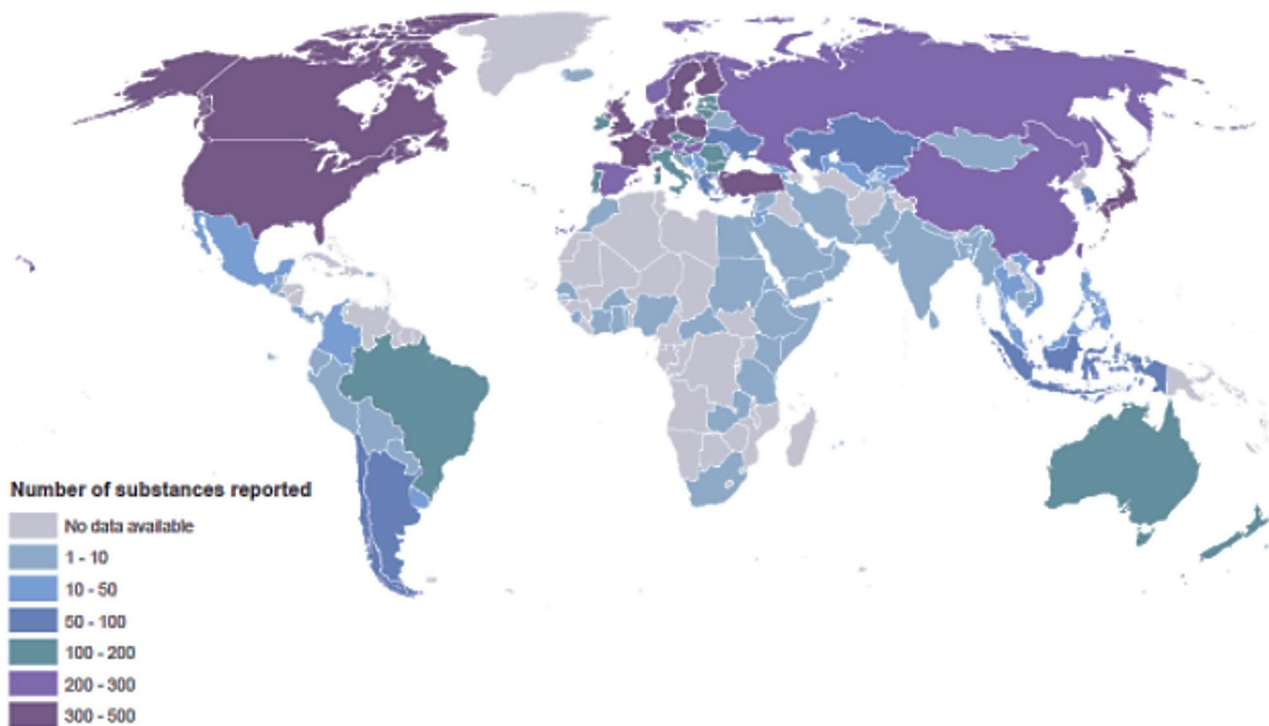


Fig. 4 Global emergence of new psychoactive substances up to December 2020 (UNODC 2020)

Conventions on Psychotropic Substances and Illicit Traffic in Narcotic Drugs and Psychotropic Substances in 1971 and 1988, respectively (Feng et al. 2017).

However, these international drug laws were later limited because they excluded several psychoactive plants that have been proven to pose threats to public health (Fasakin et al. 2021). These excluded plants were termed “new psychoactive plants” (NPP) by the United Nation Office on Drugs and Crime (UNODC), with 22 plants named among the 1047 psychoactive substances reported in 126 countries and territories by governments, institutes, and private organizations to the UNODC Early Warning Advisory (EWA) as of December 2020 (UNODC 2020). However, the word “new” does not imply a new invention or discovery in this context, but substances that international drug laws do not prohibit. The global emergence of new psychoactive substances as of December 2020 is represented in Fig. 4.

Cannabis sativa

The scientific classification of *C. sativa* (Fig. 5) is as shown in Table 1. The earliest report of the plant is dated back to 2737 BC in China during the reign of Chinese Emperor Fu His ca.) (Szaflarski and Bebin 2014). However, archaeological studies have shown it existed in Taiwan about 12,000 years ago (Bonini et al. 2018). The plant was only used for textile and fiber production before its medicinal and recreational values

were known (Kumar et al. 2021). It is even the oldest of all known cultivated fiber plants (Cherney and Small 2016). The medicinal use of *C. sativa* dates back to over 5000 years ago when it was prescribed for rheumatism, malaria, and fatigue by the then emperor Chen Nung (Bonini et al. 2018). The plant was termed “Good for the Old and Young” in an advertisement by Norman Rockwell.

Cannabis sativa was unregulated until 1906, when it was prohibited from cultivation and use under the Pure Food and Drug Act, a decision that was based on reports of the Indian Hemp Drugs Commission (set up by the British government) between 1893 and 1894 (Szaflarski and Bebin 2014). Despite antagonisms from American Medical Association (AMA), *C. sativa* was prohibited for cultivation and use by the United States government in 1937 and then after, in most world countries, such as Nigeria (Kumar et al. 2021). However, changes in most countries’ political climates have triggered several reforms and positive approaches towards legalizing *C. sativa* for medicinal and industrial but not recreational use. Examples include agitations to end the Federal Marijuana Prohibition Act of 2013 (H.R. 499) in the USA (Szaflarski and Bebin 2014); agitations in Colorado for the legalization of *C. sativa* use (Annas 2014); the deletion of *C. sativa*, and its related substances from the schedule IV of the 1961 convention, though still retained in schedule I of the convention act (Newman et al. 2021); and the move in Nigeria led by Ondo State Governor Akeredolu for legalization of

Fig. 5 *Cannabis sativa*

the plant for industrial and medicinal use (Akingboye 2019; Olasupo 2019), etc.

It was introduced into Nigeria by sailors and soldiers who returned from North Africa, the Far, and the Middle East during and after the era of the Second World War (Duvall 2016). Local names in Nigeria are Igbó (Yoruba), wi-wi (Hausa), and Nwonkaka (Ibo), with Indian hemp or marijuana being the prevalent general name in Nigeria. *C. sativa* is referred to as hemp industrially and marijuana/*Cannabis* medicinally/recreationally. *C. sativa* is combined with tramadol, codeine, and colorant drinks for the production of

Skushies/Scoochies (a psychoactive cocktail drink) in Nigeria. However, when the colorant drink is replaced by vodka, the cocktail drink is called *Gutter water* (Dumbili et al. 2021).

Despite over 30 years of the nation's application of the Drug Prohibition Policy on *C. sativa* recreational use and the plant being the most seized substance of abuse by National Drug Law Enforcement Agency (NDLEA), its trafficking and abuse are ever intensifying, with the country being the 8th highest *Cannabis* consumer globally and 1st in Africa (Alemika 2018; Goar 2021). *C. sativa* cultivation is well established nationwide as the geographical and climatic

Table 1 The scientific classification of Nigerian psychoactive plants

Classification	<i>Cannabis sativa</i>	<i>Datura Stramonium</i>	<i>Nicotiana tabacum</i>	<i>Carica papaya</i>
Domain	Eukaryota	Eukaryota	Eukaryota	Eukaryota
Kingdom	Plantae	Plantae	Plantae	Plantae
Phylum	Tracheophytes	Tracheophytes	Tracheophytes	Tracheophytes
Subphylum	Angiosperms	Angiosperms	Angiosperms	Angiosperms
Class	Eudicots	Eudicots	Eudicots	Eudicots
Sub Class	Rosids	Asterids	Asterids	Rosids
Order	Rosales	Solanales	Solanales	Brassicales
Family	Cannabaceae	Solanaceae	Solanaceae	Caricaceae
Genus	<i>Cannabis</i>	<i>Datura</i>	<i>Nicotiana</i>	<i>Carica</i>
Species	<i>C. sativa</i>	<i>D. stramonium</i>	<i>N. tabacum</i>	<i>C. papaya</i>

factors of the country provide a favorable environment for its cultivation. In 2016, *C. sativa* plantations covering 718 hectares nationwide and 187,394 kg of *C. sativa* substances were destroyed, but this was less effective in alleviating its abuse as 10.8% of the nation's adult population was still recorded by UNODC in 2018 to be an active *Cannabis* user. This prevalence was probably due to the resilience of the plant's cultivators to produce more *Cannabis* plants, as the cultivation of *Cannabis* is their primary source of income (Afsahi and Mouna 2014; Laudati 2016). In folklore, the routes of exposure are smoking, inhalation, drinking, chewing, and dipping.

Mechanism of action

Over 750 natural compounds have been identified from the plant *C. sativa*. Of these natural compounds, over 100 are phytocannabinoids (Hanus et al. 2016) which can be divided into different subclasses of Cannabigerol (CBG), Cannabichromene (CBC), Cannabidiol (CBD), Tetrahydrocannabinol (THC), Δ -9-tetrahydrocannabivarin (D9-THCV), Cannabicyclol (CBL), and Cannabinol (CBN) types (Sirikantaramas and Taura 2017; Bonini et al. 2018). More than 200 terpenoids, implicated for the fragrance and critical component in modulating strain-specific physiological properties, have been detected in the plant (Booth et al. 2017). It also possesses other secondary metabolites such as about 20 flavonoids, two lignans (lignanamides and phenolic amides), and three steroids (Kumar et al. 2021). *C. sativa* has been observed to improve appetite and food intake in human immunodeficiency virus (HIV) patients by elevating leptin and ghrelin hormones and depleting peptide tyrosine hormone required for appetite regulation (Birdsall et al. 2016). The ability of the plant to modulate angiotensin-converting enzyme II (ACE-2) receptors required by the severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) for pathogenesis, and minimize the virus impact and severity by suppressing the protein responsible for its ribonucleic acid (RNA) replication, thereby preventing the virus from penetrating host cells (Wang et al. 2020), have resulted to the plant being touted as a potent drug for treating SARS-CoV-2 patients.

Of all the compounds identified in *C. sativa*, the psychotropic constituent implicated for its psychoactivity is the Δ -9-tetrahydrocannabinol (Δ THC). Δ -9-tetrahydrocannabinol is primarily metabolized by cytochrome P-450 (CYP2C19 and CYP2C9) to 11-hydroxy-THC (which has an equipotent psychoactivity). Then, 11-hydroxy-THC is rapidly metabolized to 11-nor-9-carboxy-THC that glucuronates to THC-COOH beta glucuronide (non-psychoactive) and other non-cannabinoid metabolites (alkenes and terpenes) and then expelled via urine and fecal matter (Omara et al. 2021). The oxidation of 7- and 8- positions of Δ THC

is catalyzed by human liver CYP3A4 (Cunha-Oliveira et al. 2013). Meanwhile, cannabidiol (CBD) is hydroxylated by isozymes cytochrome P-450 3A4 (CYP3A4) and CYP2C19 to 7-hydroxy cannabidiol (7-OH-CBD) and then expelled via urine and fecal matter (Kis et al. 2019).

The introduction of Δ THC into the biological system elevates dopamine release, leading to anxiolytic effects and euphoric sensations (Cohen et al. 2017). Δ -9-tetrahydrocannabinol (Δ THC) activation of cannabinoid receptor type 1 (CB1) receptors in *Cannabis sativa* has been linked to psychoactive effects, the opening of K^+ channels, and the inhibition of adenylate cyclase and N^- and P/Q-type voltage-activated Ca^{2+} channels. In contrast, cannabidiol (CBD) activations of cannabinoid receptor type 2 (CB2) receptors are not (Volkow et al. 2017). This ability of *C. sativa* to activate CB1 receptors has touted its potential to act as an antidepressant and, alleviate depression and anxiety, since most depressive symptoms show blockage of the CB1 receptors. This anti-depressive ability was established by Fasakin et al. (2022a) to be elicited via the neurotransmitter, neurotrophic, and neuroinflammatory systems. Walsh et al. (2017) also observed that 7 out of 9 researches on depression-based cross-sectional studies demonstrated improvements in depressive symptoms.

Activation of CB1 receptors by *C. sativa* at different brain regions also triggers other actions, such as (a) inhibition of γ -aminobutyric acid (GABA) release at the GABAergic neurons terminals of the hippocampus, leading to long-term potentiation in CA1 neurons and disinhibition of dopaminergic neurons (that results in elevated synaptic dopamine concentrations), (b) intense firing of corticospinal neurons at the striatal, which results in excess glutamate release, the influx of Ca^{2+} and consequent activation of endocannabinoid synthesis at medium-sized striatal spiny neurons, and (c) regulation of inhibitory and excitatory neurotransmitter balance (Bouchet and Ingram 2020). Stimulation of CB1 receptors by adenylyl cyclase inhibitor activation results in inhibiting cyclic adenosine monophosphate pathway production while stimulation of CB2 receptors blocks tissue damage and inflammatory activities (Archie and Cucullo 2019).

Exposure of aged mice to Δ THC reverses age-related cognitive performance decline, elevates synaptic marker proteins expression, and improves hippocampal spine density via glutamatergic CB1 receptor-dependent stimulation (Bilkei-Gorzo et al. 2017). Δ -9-tetrahydrocannabinol (Δ THC) has also been observed to help treat glaucoma and increase acquired immunodeficiency syndrome (AIDS) victims' appetite to maintain their body size (Datta et al. 2021). Synergistically, cannabidiol (CBD) combines with Δ THC to act as anticonvulsants in the management of epilepsy (Shirazi-zand et al. 2013). Mechanism of action was through concurrent modulation and inhibition of neuronal hyperexcitability by CBD and the inhibitory effects of Δ THC on the N-arachidonylethanolamine (AEA) endogenous ligands and the CB1 receptors. CBD offsets the

neurotoxicity and psychoactivity associated with Δ THC (Chye et al. 2021). This indicates that *C. sativa* strains with high CBD and low Δ THC concentrations will be less toxic and psychoactive than low CBD and highly concentrated Δ THC plants. Both phytocannabinoids have also been shown to synergistically exert pain relief using animal models (Romero-Sandoval et al. 2018).

Cannabidiol (CBD) also inhibits tau protein hyperphosphorylation, acetylcholinesterase activity, and expression of β -amyloid (Vallée et al. 2017; Furqan et al. 2020; Hao and Feng 2021). The pharmacological mechanism of action is implicated in the multifaceted pathogenesis of Alzheimer's disease. Cannabidiol (CBD) influences peroxisome proliferator-activated receptor γ (PPAR- γ) and acts as a PPAR- γ agonist (Ożarowski et al. 2021), reducing inflammation and amyloid plaque in Alzheimer's disease conditions. The agonist of this receptor by CBD also enhances memory and cognitive function in Alzheimer's disease patients. The ability of CBD to induce antidepressant effects and deoxyribonucleic acid methyltransferase (DNMT) activity alteration in the prefrontal cortex (PFC), as well as global deoxyribonucleic acid (DNA) methylation at the hippocampus and PFC, have also been established (Sales et al. 2020). Exposure to CBD also elevates amyloid precursor protein ubiquitination, improves A β peptide clearance, and exhibits antiapoptotic, anti-gliosis, and anti-inflammatory properties (Esposito et al. 2011; Scuderi et al. 2014). Interestingly, analysis of *C. sativa* addicted humans showed CBD binds to cholinesterases (acetylcholinesterase and butyrylcholinesterase) to inhibit the enzymes activities (Ożarowski et al. 2021).

Furthermore, CBD inhibits glial proinflammatory cytokine, inducible nitric oxide synthase, and glial fibrillary acidic protein expression in a dose-dependent manner (Esposito et al. 2011). CBD inhibits pro-angiogenic factors and cancer cell migration and growth in neural system cancers, influences F-actin integrity disruption, and promotes cyclin dependent kinase inhibitor 1A (CDKN1A) (p21) protein expression (Ożarowski et al. 2021). Cannabidiol (CBD) can also activate the intrinsic apoptotic pathway, reduce cytochrome c release into the cytosol and mitochondrial Ca^{2+} overload and membrane potential by inhibiting Bcl-2 and beclin-1 interactions (Shrivastava et al. 2011).

Toxicity

The main toxic component of *C. sativa* is Δ THC which was isolated by Professor Mechoulam and colleagues in 1964, while the system it activates, the endocannabinoid system was identified during the 80 s and 90 s decades (Mechoulam and Parker 2013). The behavioral, cognitive, and psychosocial toxicity of *C. sativa* has been observed to be transient and mild (Szaflarski and Bebin 2014) due to CBD offsetting the psychoactive and neurotoxic effects of Δ THC. Interestingly,

an author even suggested that it may be the least dangerous of most psychoactive plants (Faria 2021), with only a few case reports and a series of paediatric *C. sativa* intoxication being ever documented (Wong and Baum 2019). Although, lack of sober mental control after exposure to recreational *C. sativa* has been proven to increase road accidents prevalence, as a result of *C. sativa* smokers being exposed to five times carbon monoxide and tar deposition in comparison to *N. tabacum* cigarette smoke due to having to hold longer breath times, deeper inhalation and lack of *C. sativa* cigarette filters (Omara et al. 2021). The neurotoxic effects of *C. sativa* have been observed to differ with acute, subacute/sub chronic and chronic exposures, the ratio of Δ THC to CBD, mode of exposure, initiation age of usage, and the presence of contaminants (Szaflarski and Bebin 2014).

During *C. sativa* exposure, Δ THC crosses the blood–brain barrier (BBB), reaches peak concentration within a few minutes of exposure due to its high lipid solubility, has a half-life of about seven days, and takes approximately 30 days to be eliminated from the user's body system (Calapai et al. 2020). Exposure to *C. sativa* is characterized by euphoria, jocularity, anxiety, and relaxation, though these effects are rapidly replaced with hallucinations, paranoia, and confusion as the dose increases. At very high doses, exposure to *C. sativa* potentiates reversible cerebral vasoconstriction syndrome. Extreme complications such as haemorrhagic stroke and *Cannabis*-related ischemic via vasospastic mechanism have been observed within half-an-hour of *C. sativa* use (Wolff et al. 2013). Another toxicological mechanism employed by *C. sativa* is increased dopamine production, which inhibits acetylcholine secretion and thereby decreases glutamatergic synaptic transmission, resulting in brain function aberrations (Bloomfield et al. 2016).

Additionally, exposure to *C. sativa* during pregnancy results in weakened dexterity and visualization, with a high probability of giving birth to offspring susceptible to abnormal behaviors (Archie and Cucullo 2019). Exposure to *C. sativa* during the early stage of development has been associated with poor personality (Maldonado and Torrens 2020), educational outcomes (Lorenzetti et al. 2020), cognitive performance and working memory (Prini et al. 2020), task execution, and intelligence quotient (Pope et al. 2003), task planning (Fontes et al. 2011), visual attention, and increased blood oxygenation level-dependent (BOLD) activation at the frontoparietal regions during adulthood (Tervo-Clemmens et al. 2018). The effects of acute and chronic *C. sativa* exposure are not just limited to prenatal and neonate brains alone; their impact on the developing and mature brain has also been established (Batalla et al. 2013). Heavy *C. sativa* uses during adolescence was also observed to deplete the intelligence quotient by 4.1 points. In contrast, light *C. sativa* use and non-users significantly increased intelligence quotient than heavy users in the same study (Meier et al. 2012).

Datura stramonium

The scientific classification of *Datura stramonium* (Fig. 6) is as shown in Table 1. The plant is reported to be of Central American origin likely. It was introduced to Nigeria and is considered one of the world's most widespread weeds (FAO and WHO 2020a). It is classified as one of the oldest and most abused psychoactive plants (Disel et al. 2015). The plant's genus name, *Datura*, came up in 1662 from the Hindi word *Dhatūrā* and the species name in English was Jamestown weed, before being transformed to jimson weed (Furbee 2009). Globally, the plant is known as angel trumpet or tear, devil trumpet, green dragon, jimson weed, thorn apple, etc. (Krenzelok 2010). It is known as Gegemu (Yoruba) or Zakami (Hausa) in Nigeria's local languages.

D. stramonium was used in ancient times as a drug due to its potency as a pain reliever and sleep inducer (Julyan 2014). It was even documented that the god lord Shiva was addicted to *D. stramonium* and *C. sativa* smoking (Soni et al. 2012). It is locally employed to treat various ailments and as a hallucinogen to trigger intense visions when taken entheogenically. It was used in ancient times for witches' brew and love potion essential ingredients (Preissel and Hans-George 2002). Historically, *D. stramonium* are mixed with *Nicotiana tabacum* by armed robbers and offered forcefully to sedate and cause anterograde amnesia in their robbery victims (Saussereau et al. 2014).

D. stramonium has been reported for recreational use in Nigeria, with reports of 3.8–40.1% prevalence observed among respondents (Adegoke and Alo 2013; Adesanya et al. 2020). Despite the high prevalence of its recreational use, its numerous occurrences as food contaminants are the



Fig. 6 *Datura stramonium*

primary source of severe intoxications and deaths (Devi et al. 2011; Ekanem et al. 2016b). In folklore, *D. stramonium* seeds and leaves are usually soaked in alcoholic solvents for hours or days and drunk as a beverage. It is also used to increase the intoxication potency of most alcoholic drinks (Ekanem et al. 2016a). The Fulani tribe of Nigeria uses it to prepare porridge served during public stroke beating of suitors (*Sharo/Shadi*) during marriage ceremonies (Abdu et al. 2020). The Fulfulde tribe of Nigeria also employs *D. stramonium* brew to elevate young men's pain tolerance and courage before entering fighting contests. A few others have reported the seeds and leave been chewed or smoked for recreational purposes (Soni et al. 2012; Trancă et al. 2017). Although it is a licit plant in Nigeria, some countries prohibit its cultivation and trading (Preissel and Hans-George 2002).

Mechanism of action

D. stramonium belongs to the family Solanaceae. Over seventy (70) alkaloids have been identified in the plant (El Bazaoui et al. 2011), with the different seasons, climate, and location of cultivation posing different alkaloid patterns (Berkov et al. 2006; Krenzelok 2010). The alkaloids in *D. stramonium* implicated for its neuromodulatory effects are hyoscyamine, scopolamine, and atropine (Oseni et al. 2011; Shagal et al. 2012). These alkaloids are anticholinergic compounds as they cross the blood–brain barrier to bind with muscarinic acetylcholine receptors and act as competitive antagonists at these receptors. The muscarinic acetylcholine receptors subtypes antagonized during *D. stramonium* exposure are the M2, M4, and M5 receptors. These alkaloids alter the imbalance between adrenergic and cholinergic regulation of brain function. Atropine has been observed to stimulate the central nervous system. In contrast, scopolamine depresses the central nervous system (Brown and Taylor 2006).

D. stramonium anticholinergic properties have potentiated its use as a substitute for atropine in managing muscarinic symptoms during organophosphate toxicity (Soni et al. 2012). The plant has varying therapeutic potentials, such as treatment of inflammation, swellings and bruising, wounds, gout and rheumatism, sciatica, and toothache, in folklore medicine. Still, they have all been eclipsed by the toxicity and hazards of plant ingestion (Alwirfli et al. 2021). It was observed that chronic exposure to *D. stramonium* as high doses for four (4) weeks significantly elevated CREB expression in male animals but depleted CREB expression in female animals (Ekanem et al. 2016b). This result agrees with earlier observations that the mechanism of action of *D. stramonium* is sex and age-dependent, with the female species being observed to respond more and sometimes different than the male species (Ekanem et al. 2015b). The alteration of CREB protein expression at the molecular level has

been implicated as the paradigm underlining *D. stramonium* addiction despite its adverse effects (Wang et al. 2009).

Toxicity

Only a few psychoactive substances have been reported for severe negative recreational experiences (including comas and deaths) as *D. stramonium*. Symptoms of severe toxicity appear within 30 to 60 min of ingestion and could last for days as a result of the plant's ability to delay gastric absorption and to empty by inhibiting gastric motility via its anticholinergic effect, thereby increasing the transit time of the plant in the victim's gastrointestinal tract, resulting in extension of toxidromes duration (Kuete 2014; Adesanya et al. 2020). Children and teenagers have shown more susceptibility to *D. stramonium* toxicity, with very low doses resulting in very profound central and peripheral nervous system effects (Rakotomavo et al. 2014). Despite the scarcity of death associated with exposure to *D. stramonium*, ingestion of about 125 seeds has been reported to cause death via heart failure (Soni et al. 2012). The first recorded poisoning was in 1676 when soldiers under the command of Captain John Smith during the Bacon Rebellion prepared a salad comprising of *D. stramonium* and immediately began hallucinating (Furbee 2009). The plant has also been shown to contain gamma – 1 – glutamyl – aspartate, a compound that has been implicated in permanent short-term memory loss and impaired learning (Ekanem et al. 2016a). Ingestion of the plant at high doses has been observed to result in insanity in humans (Singh and Singh 2013). *D. stramonium* was thus listed by the World Health Organization (WHO) as a major cause of psychiatric illness and mental disorders. It is even a popular poison for murder and suicide (Oseni et al. 2011).

All the plant parts have been observed to contain lethal levels of tropane alkaloids scopolamine, hyoscyamine, and atropine which block the neurovegetative cholinergic system through competitive antagonistic actions on the central and peripheral muscarinic cholinergic receptors (Halpern 2004). They are therefore grouped under anticholinergics or deliriants (Ademiluyi et al. 2016a, b), which when ingested causes mydriasis, dry skin, tachycardia, and other fatal consequences. During the first few weeks of sprouting, *D. stramonium* mainly contains scopolamine, but as they mature, hyoscyamine begins to predominate (Furbee 2009). Uncontrolled inhibition of cholinesterases results in excessive choline accumulation at the synaptic cleft, thereby overstimulation of cholinergic neurons (Rodrigues et al. 2011). Excessive stimulation of the cholinergic neurons has been implicated in neurodegeneration syndromes such as hallucination, psychosis, tachycardia, severe mydriasis, delirium, hyperthermia, bizarre behavior, and in extreme cases, the organism's death (Maibam et al. 2012; Miguel et al. 2016). Another system implicated in the

neurotoxicity of *D. stramonium* is the monoaminergic system of neurotransmission (Fasakin et al. 2021). Exposure to the plant can cause excessive inhibition of the two isoforms (A and B) of monoamine oxidase (MAO), which are responsible for the oxidative deamination of biogenic amines (noradrenaline, serotonin, dopamine, tyramine, etc.) (Ademosun et al. 2022; Fasakin et al. 2022a). Although MAO inhibitors are therapeutic, the excessive inhibition of MAO by *D. stramonium* leads to neurotoxicological complications such as hypertensive crisis and serotonin toxicity (Ademiluyi et al. 2016b).

Another mechanism of *D. stramonium* neurotoxicity is via impairment of the purinergic system of neurotransmission (Ademiluyi et al. 2016a). Enzymes involved in the purinergic system of neurotransmission are the ecto-nucleotide pyrophosphatase/phosphodiesterase, ecto-nucleoside triphosphate diphosphohydrolase, ecto-5'-nucleotidase, alkaline phosphatase, and Na⁺/K⁺ATPase (Yegutkin 2008; Oyeleye et al. 2022). Dysfunction of the Na⁺/K⁺ATPase enzyme, as exhibited by the plant, has been implicated in the distortion of Na⁺/K⁺ equilibrium. This mechanism has been shown to result in nerve endings depolarization coupled with Ca²⁺ influx into brain cells, leading to excess neurotransmitters release and swelling of the neurons (de Lores Arnaiz and Ordieres 2014; Fasakin et al. 2021). Inhibition of ecto-nucleoside triphosphate diphosphohydrolase by *D. stramonium* impairs neuronal adenosine triphosphate (ATP) hydrolysis. A mechanism that has been shown to result in excessive extracellular ATP accumulation, P2 purinergic receptors overstimulation, and consequently, impairment of the purinergic neurotransmission system (Ademiluyi et al. 2016a). Furthermore, ecto-5'-nucleotidase inhibition by *D. stramonium* has been implicated in extracellular adenosine levels depletion, resulting in adrenergic neurotransmission and memory impairment (Marisco et al. 2013; Fasakin et al. 2021).

Interestingly, *D. stramonium* also significantly elevates the activity of tissue non-specific alkaline phosphatase (TNSAP), the enzyme involved in enhancing the toxicity of extracellular tau protein, resulting in the progression of Alzheimer's disease (Kellett and Hooper 2015; Vardy et al. 2011). Furthermore, *D. stramonium* has been shown to cause neurotoxicity via excessive generation of free radicals and impairment of the antioxidant system (Ogunsuyi et al. 2020; Fasakin et al. 2022a). This excessive generation of free radicals is marked by a high level of lipid peroxidation, Na⁺/K⁺ATPase impaired function, activation of glial cells, misfolded proteins, membrane configuration derangement, cellular apoptosis, and dysfunction of cellular mitochondria (Fulda et al. 2010; Ogunmoyole et al. 2019). The activities and levels of antioxidants were depleted, resulting in the depletion of neuronal integrity and loss of cognitive functions and neuronal cell deaths (Wang et al. 2014).

Neurotoxicity of *D. stramonium* has also been established via alteration of the cAMP response element-binding protein (CREB) gene expression. Elevated CREB gene expression

observed in male rats was suggested to be due to excessive expression of the inactive form of CREB protein or the CREB-2 isoform. This process has been implicated in neurodegeneration to frontal cortex and hippocampal neurons (Ekanem et al. 2016b; Fasakin et al. 2022a). At the same time, the depleted CREB gene expression observed in female rats was associated with neurodegeneration via excessive inhibition of CREB function and expression in pyramidal neurons, which results in excessive loss of cornu ammonis (CA) 1 subfield neurons (Dragana et al. 2009). Similar neurodegeneration was observed in the frontal cortex of female rats, where depletion in CREB expression and its integrative role was observed during *D. stramonium* exposure (Ekanem et al. 2016b).

D. stramonium toxicity has also been observed to mediate cerebellar dysfunctions in granular cell parallel fibers and Purkinje cells of the cerebellum, resulting in degeneration and atrophy of the granule cells' parallel fibers, which are usually marked by hypoplasia, dyssynergia, and disequilibrium (Ekanem et al. 2015a). This dysfunction was also implicated in learning, memory, and motor impairments observed during the study. Similar cerebellar dysfunction was also observed by Flegel et al. (2007) in their research using Bavarian Mountain dogs as experimental animals. Another study even observed the same effect using human specimens (Forrester 2006). It is therefore noteworthy that *D. stramonium* neurotoxicity can occur almost in all animals.

***Nicotiana tabacum* (tobacco)**

The scientific classification of *N. tabacum* (Fig. 7) is as shown in Table 1. Its origin stretched back to 6000 BC and was introduced into Nigeria in 1904 (Klein and Resnick 2021). Local Nigerian names are Taba (Yoruba), Utaba (Igbo), and Taba (Hausa). *N. tabacum* use is the leading cause of preventable death, with around 6 million deaths globally per year which is expected to surge to around 8 million in 2030 if the prevalence use continues (Okunna 2018). Nigeria has one of the leading *N. tabacum* markets in Africa, with a prevalence of over 18 billion tobacco cigarettes sales annually. Accounting for about 931 million US dollars per year, an indication that the implementation and effective operationalization of the World Health Organization Framework Convention on Tobacco Control (FCTC) of 2005 and the National Tobacco Act of 2015 is still a mirage in the country (WHO 2015; Ayodapo and Ibisola 2021). It is a psychoactive plant readily available in every corner of the earth (Tiwari et al. 2020).

Statistically, 55.3% of active tobacco smokers smoke their first tobacco for the day within 30 min of their waking up and consume an average of 10 tobacco cigarettes per day per person which accounted for approximately 110 million tobacco cigarettes per day and about 40 billion tobacco cigarettes in the



Fig. 7 *Nicotiana tabacum*

year 2015 alone (Adeloye et al. 2019). In 2015, the prevalence of active tobacco smokers in Nigeria ranged from 1.2% in Yaba, Lagos state, to 55.5% in Amassoma, Delta state (Dania et al. 2015; Owonaro and Eniojukan 2015). Another study in 2019 observed that the average prevalence of active tobacco smokers among adult Nigerians was 8.8%, a high prevalence compared to the estimation of 4% active tobacco smoking adult Nigerian population in 2012 (Adeloye et al. 2019; Adeniji et al. 2016). In 2019, tobacco smoking prevalence by geographical location was observed to be North-east (32.1%), South-south (13.0%), North-central (10.3%), South-west (8.9%), South-east (8.6%), and North-west (5.4%) (Adeloye et al. 2019), a deviation from that observed by Kale et al. in 2012, in which North-central had the highest prevalence of tobacco product consumers at 5.2%. However, just 1.5% of Nigerian adults were active consumers of smokeless tobacco, with the highest majority occurring within 45 to 64 years (Kale et al. 2012). *N. tabacum* can also be smoked with *D. stramonium* to increase its entheogenic effects (Carod-Artal 2015). Aside from smoking, tobacco is ingested via chewing (fresh leaves, chewing gum, etc.), inhalation, dipping, or drinking.

Mechanisms of action

The psychoactive constituents of *N. tabacum* are the potent parasympathomimetic alkaloid, nicotine, cotinine, anabasine, nor nicotine, etc., that synergistically work to mediate the dependence and tolerance observed among the plant recreational users. Nicotine was first isolated in 1828 from *N. tabacum* by chemist Karl Ludwig Reimann and physician Wilhelm Heinrich Posselt in Lille, France (Rai and

Tewari 2018). Nicotine addiction has been observed to be the most difficult to break (Kuete 2014). Nicotine ranges between 0.6 and 3% of *N. tabacum* dry weight (Rai and Tewari 2018). At a lower dose (about 1 mg), nicotine is a stimulant, while at high doses (30 to 60 mg), it causes severe toxicity and lethal effects (Kuete 2014). The impact of *N. tabacum* and nicotine on the central nervous system was observed to be sex and age-dependent, with the neurotoxic effects more pronounced in males than their female counterparts, while the prenatal and adolescent brain was also observed to be more vulnerable in comparison to the adult brain (Schochet et al. 2005; Slotkin et al. 2015; Fasakin et al. 2022a). When inhaled, nicotine is quickly absorbed and reaches the brain in about 7 s with about 2 h half-life in the user's system (Hukkanen et al. 2005). This potency has stimulated its use as an insecticide in folklore.

The mesolimbic dopamine system is the primary neurotransmission system through which nicotine expresses its psychoactivity. Nicotine exposure stimulates dopamine release from the mesolimbic system neurons of the VTA and terminates it at the NAc (Picciotto and Mineur 2014). Meanwhile, chronic nicotine exposure has been implicated in elevating (a) VTA-dopamine responsiveness to nicotine; (b) nicotine-induced dopamine release selectively at the medial prefrontal cortex (mPFC); (c) nicotine-induced *c-fos* expression at the medial prefrontal cortex (mPFC) that encompasses D1-dopamine receptor activation; and (d) arc and p53 upregulation at the cerebral cortex, hippocampus, and midbrain (Schochet et al. 2005). Furthermore, nicotine-induced activation of the mesolimbic dopamine system has been observed to entail concomitant NMDA receptor activation at the ventral tegmental area (VTA) via elevation in excitatory amino acid (EAA) concentrations (Picciotto and Mineur 2014). Nicotine can also promote dopamine release by elevating tyrosine hydroxylase expression and release via somatodendritic nAChRs activation at the mesolimbic and nigrostriatal dopamine pathways. Other neuronal (glutamate, glucocorticoid, opioid, and serotonin) systems related to substance dependence are also modulated during nicotine exposure.

Another alkaloid involved in mesolimbic dopamine system activation during *N. tabacum* exposure is cotinine. Cotinine increases dopamine release through a Ca^{2+} -dependent pathway (Tiwari et al. 2020). Aside from the mesolimbic dopamine system, the serotonergic transmission system is also altered during *N. tabacum* exposure. Exposure to *N. tabacum* inhibits the application of hippocampus serotonin via selective enhancement of 5-HT_{1A} receptors concentrations in brain segments (Yue and Edward 2008). The hippocampus has been proven to obtain its serotonergic innervations through the median raphe nucleus. Monoamine oxidase (MAO), the enzyme implicated in the metabolism of dopamine, serotonin, and other biogenic amines, is another

enzyme inhibited due to *N. tabacum* exposure (Fasakin et al. 2021; Ademosun et al. 2022). The inhibition of the two isoforms of MAO (A and B) was observed to result in elevated brain dopaminergic release (Tiwari et al. 2020). Interestingly, nicotine has been proven not to alter MAO activity, indicating that another *N. tabacum* alkaloid aside from nicotine is involved in MAO modification and the addiction and dependence observed among *N. tabacum* users (Bierut et al. 2008; Julie et al. 2017).

Extracellular concentrations of glutamate were also observed to be elevated as a result of exposure to nicotine (Fasakin et al. 2022a). The elevation of glutamate was observed to be initiated as a result of sensitization of presynaptic $\alpha 7^*$ nAChRs that mediates Ca^{2+} elevation at the glutamatergic presynaptic terminals, which in turn elevates the release of glutamate and excitation of dopaminergic neurons as well as desensitization of $\beta 2^*$ nAChRs at the dopaminergic neurons (Pidoplichko et al. 2004). This process was observed to favor long-term synaptic plasticity that mediates glutamatergic release. Presynaptic glutamatergic excitation was also observed to coincidentally occur alongside an excessive postsynaptic response to mediate Ca^{2+} signalling via NMDA-type glutamate receptors that both trigger long-term potentiation (LTP) (Mansvelder and McGehee 2002; Mansvelder et al. 2002). Afterwards, non- $\alpha 7$ subtypes were observed to be desensitized, resulting in decreased inhibition onto dopaminergic neurons by GABAergic neurons, while the $\alpha 7^*$ nAChRs located on presynaptic glutamate terminals remains sensitized. This leads to enhanced glutamatergic excitation in as much nicotine signals are still present and the subsequent prolonged dopamine signalling at the NAc, implicated as a significant component of the *N. tabacum* addiction process (Pidoplichko et al. 2004).

During exposure to *N. tabacum*, nicotine crosses the blood–brain barrier (BBB) in less than 10 s. It binds agonistically to nicotinic acetylcholine receptors (nAChRs) at the ganglia, neuromuscular junctions, and central nervous system, resulting in activation of ventral tegmental area (VTA) and substantia nigra compacta (SNc) neurons leading to dopamine release at the nucleus accumbens (NAc) (Pidoplichko et al. 2004). Upon binding of nicotine to the nAChRs, the nAChRs are stimulated, but a prolonged depolarization which results in receptor paralysis follows after some minutes except for at nAChR $\alpha 9$ and nAChR $\alpha 10$ sub-units where it acts as receptor antagonist (Klaassen 2008; Rai and Tewari 2018). Presynaptic nAChRs excitation elicits acetylcholine discharge and metabolism. At the same time, maximum nicotine sensitivity was observed on the $\alpha 4\text{-}\beta$ subunit arrangement, which was also implicated in the alkaloid's main addictive behavior property (Tiwari et al. 2020). Long-term exposure to *N. tabacum* was also shown to result in receptor inactivation, and consequent nAChRs situate upregulations. Furthermore, receptors inactivation can mediate a long-term effect on the standard nicotinic mechanism

activated by the endogenous cholinergic activity (Pidoplichko et al. 2004).

Interestingly, nicotine also causes inhibition of the chromatin-modifying enzymes (class 1 and 2 histone deacetylases), a process that improves the potential of cocaine to mediate addiction (Volkow 2011). Furthermore, fibroblast growth factor required for neuronal proliferation maintenance, bone morphogenic proteins, and ciliary neurotrophic factor needed for astrocyte differentiation, and brain-derived growth factor (BDGF), platelet-derived growth factor (PDGF), and neurotrophin-3 required for modulating neuronal differentiation, have all been observed to be increased during nicotine exposure, and alter gene expression and cascades of second messengers (deBry and Tiffany 2008). Although, modulating the trajectories of development and automated cell death in adolescents during nicotine exposure may result in imbalances in the final neuronal architecture (Abreu-Villaca et al. 2003).

Toxicity

This psychoactive plant has nicotine and anabasine as their major toxic alkaloids and can be lethal to humans at specific doses. Exposure to *N. tabacum* smoking has been implicated as the single primary source of toxic chemical exposure to humans (Swan and Lessov-Schlaggar 2007), with WHO forecasting this exposure to result in about nine (9) million deaths globally in the year 2030 (Mathers and Loncar 2006). Noteworthy, *N. tabacum* smoke extracts were observed to be about ten times potent in upsetting neurotoxicity compared to its alkaloid, nicotine during an in vitro study (Slotkin et al. 2014), establishing the fact that other *N. tabacum* constituents (such as anabasine, polycyclic aromatic compounds, etc.) may be involved in its neurotoxicity. The above *N. tabacum* smoke extract differs from the regular tobacco smoke in that they do not contain hydrogen cyanide and carbon monoxide (Slotkin et al. 2015). Interestingly, benzo(a)pyrene (a constituent of *N. tabacum* smoke extracts) showed a synergistic effect on the central nervous system when co-administered with nicotine (Slotkin et al. 2013), thereby substantiating the potency of *N. tabacum* smoke extracts in comparison with nicotine alone.

Furthermore, *N. tabacum* smoke extracts deplete nAChRs levels while nicotine increases their levels, posing different effects such as exacerbating the practical consequences of presynaptic shortage and compensating for the loss of presynaptic involvement. Meanwhile, the prevalence of *N. tabacum* addiction has also been higher in psychiatrically disordered individuals (e.g., schizophrenia) than healthy individuals (Ferrea and Winterer 2009). This is an indication that *N. tabacum* addiction pathophysiological mechanisms may have links with psychiatric disorders.

In a typical individual cholinergic system, about 1 mM acetylcholine is released, which acts on the nAChRs, and is rapidly metabolized by the acetylcholinesterase (deBry and

Tiffany 2008). Interestingly, nicotine enters the brain slower at about 50 to 300 mM, acts on any available nAChRs, and persists for an extended period in the system. Therefore, nicotine supersedes the regular cholinergic system activity, mediates profound nAChRs desensitization, and alters synaptic activity and development. This observation, alongside cell damage and loss to neuritic projections, validates the neurotoxic effects caused by nicotinic overstimulation and adaptive desensitization of nAChRs, resulting in cholinergic transmission alteration (Slotkin et al. 2015). Upregulation of arc, p53, and c-fos at the cerebral cortex, hippocampus, and midbrain during nicotine exposure was also consistent with the prevalence of neuronal damage (Schochet et al. 2005).

N. tabacum exposure has also been observed by Jacobsen et al. (2006) to deplete verbal working memory accuracy in dopaminergic receptor D1 (*DRD2*) 957 T allele carriers. Excessive stimulation of dopaminergic neurons observed in the 957 T allele carriers was the underlining factor behind the declined performance and efficiency exhibited by the individuals (Swan and Lessov-Schlaggar 2007). However, 957C allele carriers were unaffected when exposed to *N. tabacum*, indicating that *N. tabacum* exposure may defer in neurotoxicity pattern from one allele carrier to another. Neurotoxicity of *N. tabacum* was also observed via free radical generation, which elevates oxidative stress and depletes neural cells' antioxidant defence systems (Qiao et al. 2005).

Although nicotine improves attention and performance, prenatal exposure to *N. tabacum* causes locomotor hyperactivity and adverse cognitive effects (Bizzaro et al. 2004; Larrison et al. 2004; Zhu et al. 2012). The persistent lingering of *N. tabacum* lipophilic chemicals (e.g., polycyclic aromatic compounds) causes locomotor hyperactivity and adverse cognitive effects. Although these neurotoxicants might not necessarily reach the foetus, impairment of maternal physiology and microbiome, and thyroid function could result in the neurotoxicity. Furthermore, *N. tabacum* constituents could be carried by seminal fluid or sperm of *N. tabacum* users during sexual intercourse leading to preconceptionally toxicant exposure that may cause excessive stimulation of nAChRs in the resulting foetus, which leads to malformation of neural circuits.

Prenatal exposure to *N. tabacum* increases nicotine binding at the $\alpha 7$ and $\alpha 4\beta 2$ nAChRs of infants resulting in altered gene expression and regulation of neurotransmitters release as well as GABAergic signalling, which is characterized by abnormal synaptic plasticity and organization, auditory mental dysfunction, DNA synthesis and nAChRs decrease, abrupt infant death disorder, elevated apoptosis marker concentrations, depleted cell differentiation, and replication (Ferrea and Winterer 2009). The $\alpha 4\beta 2$ nAChR is the most abundant nAChR subtype in the brain of mammals. It has been implicated in the regulation of acetylcholine system abilities to mediate other neurotransmitters release, which

leads to alteration in cognition, mood, and the reward systems of the animal. Prenatal exposure to *N. tabacum* at lower doses than expected to impair brain growth was observed to act neuro-teratogenically by mediating mistimed and excessive cholinergic stimulation characterized by behavioral alterations (deBry and Tiffany 2008). Upregulation of the expression of the mRNA-encoding genes intricated in apoptosis and differentiation was also observed in *N. tabacum* users. Summarily, the mechanism of action underlining *N. tabacum* neurotoxicity was observed via elevated calcium loads, neurotrophic factors release and cholinergic transmission, effects on nAChRs, and depletion of antioxidant systems.

Carica papaya

Historically, *C. papaya* is native to Southern Mexico and Central America and was introduced to the African continent in the sixteenth century (Chan and Paull 2008). The plant's scientific classification is as shown in Table 1. It is known locally as Ibepe (Yoruba), Okwuru-Ezi (Igbo), and Gwanda (Hausa) in Nigerian languages. The plant is used to manage varying medical conditions such as skin ageing, inflammation, depression, impaired wound healing, cancer, and several other chronic diseases via the synergistic action of its chemical compounds such as papain, caffeic acid, α -tocopherol, benzyl isothiocyanate, kaempferol, rutin, quercetin, and myricetin (Kong et al. 2021). Despite its medical prowess, the recreational use of *C. papaya* (pawpaw) leaves as a psychoactive substance in Nigeria is gaining high prevalence and becoming an escalating national socioeconomic and health burden.

The plant has both male (flowering) (Fig. 8a) and female (fruity) (Fig. 8b) species, while the male has been preferred for recreational use in comparison to the female in folklore (Fasakin et al. 2021). The leaves are usually dried and smoked in folklore and have been viewed by recreational

users as a substitute for *C. sativa* since its cultivation and use contradict no legislative regulation (Morakinyo and Odejide 2003). Meanwhile, *C. sativa*-dependent patients who are on admission in psychiatric centers often sneak out of the centers to smoke the dried leaves of *C. papaya* (Olley 2007). A study that focused on the prevalence of substance use among undergraduate students in Lagos State University observed that as high as 31.6% of respondents had used *C. papaya* leaves as a psychoactive substance (Workneh et al. 2021). Furthermore, another study conducted purposively for the University of Ibadan University observed that 65.6% of the respondents know *C. papaya* use as a psychoactive substance, 44.8% were affirmed as lifetime users. In comparison, 43.4% and 32.4% confirms that the recreational use of *C. papaya* leaves posed the same psychoactive effects as *C. sativa* and cocaine/heroin, respectively (Olley 2007). More so, a study also observed a 9.3% recreational use of *C. papaya* leaves as a psychoactive substance among North-central Nigerian youths (Aliyu et al. 2016). Interestingly, a study focused on informal religious schools observed a 5.3% recreational use among male students aged 5 to 16 years (Abdulmalika et al. 2009). Although the alkaloids of *C. papaya* leaves are potent and can easily cross the blood–brain barrier, the primary route for recreational use is via smoking.

Mechanisms of action

The bioactive agents of *C. papaya* leaves that have been implicated in its neuromodulatory effects are its alkaloids (pseudocarpain, carpain, voacangine, and undulatine) and nicotinic acid (Owoyele et al. 2008; Adedayo et al. 2020). The alkaloid extracts of *C. papaya* modulate the monoaminergic, cholinergic, and purinergic systems of neurotransmission (Fasakin et al. 2021). The psychoactivity observed with *C. papaya* use can be linked to its neuromodulatory effects on neurotransmitters (dopamine, serotonin, norepinephrine, and

Fig. 8 **a** *Carica papaya* Male. **b** *Carica papaya* Female



choline) linked to dependence and addiction as well as psycho-stimulant effects (Banala et al. 2018; Fasakin et al. 2022a).

However, the smoking of *C. papaya* leaves has also been proven to have a stimulatory effect on the central nervous system similar to that experienced during *C. sativa* use (Olley 2007). The neuro-anti-inflammatory potential of the plant has also been studied. Mechanisms of action included lysosomal enzyme linkage inhibition, pro-inflammatory cytokine secretion, H₂O₂-induced phosphorylation of p38 and Akt, downregulation of mitogen-activated protein kinase (MAPK) pathway, attenuation of ROS production, and upregulation of antioxidant enzymes (Kong et al. 2021; Somanah et al. 2017). The immunomodulatory ability of *C. papaya* has also been shown via enhancement of AMP-activated protein kinase (AMPK) activation and inhibition of cyclooxygenase-2 expression (Zuhrotun Nisa et al. 2017).

Toxicity

Carpain, the major macrocyclic lactone alkaloid of *C. papaya* leaf, was observed to form hydrophilic interactions and hydrogen binding with the interface of choline (both acetyl- and butyryl-) acyl pocket domains and binding site, with Trp 82 of the choline forming hydrophobic interaction with carpain lactone (2.5 Å) and Val 288 of the acyl pocket-forming hydrogen bonding with the carpain carbonyl group (3.3 and 4.6 Å) (Khaw et al. 2020). This mechanism was observed to inhibit cholinesterase activities (Khaw et al. 2020). Adedayo et al. (2020) also observed that Voacangine and Undulatine are potent inhibitors of cholinesterase. Therefore, at higher doses of exposure, as observed by Fasakin et al. (2021), cholinesterase will be over inhibited, leading to excessive choline accumulation at the synaptic cleft and, finally, neurodegeneration.

Exposure to smoked *C. papaya* has also been shown to cause lesion at the fimbria-formix, a process that has been shown to result in hippocampus dysfunction. This indicates that the observed elevated lipid peroxidation in the brain of experimental animals exposed to alkaloid extracts of *C. papaya* ex vivo by Fasakin et al. (2021) may be the ordeal behind the dysfunction observed. More so, exposure to the plant's alkaloids has been implicated in the onset of necrosis by causing enlargement of the perinuclear space of neural cells' nucleus (Oyewole and Owoyele 2014). Furthermore, the study noted that the exposure to the *C. papaya* leaves caused the hippocampus cells to be less active and deplete their neurotransmitters production rate. Nissl substances reduction, magnocellular layer disruption, and vacuolations were also observed during exposure to *C. papaya* leaves to smoke.

The studies of Oyewole and Owoyele (2012, 2014) further confirm these observations, that exposure to smoked

C. papaya leaves altered anxiolytic effects and long-term spatial memory and induced ultimate changes in experimental animals' hippocampus morphology. The studies further noted that smoking *C. papaya* leaves could cause neurons to be less active and deplete their neurotransmitters production rate, indicating that ingestion of high doses of *C. papaya* leaves will mediate the exact mechanism of action.

Limitation of the study

Manihot esculenta and *Moringa oleifera* were listed as plants that are recreationally used in Nigeria (Abdurahman et al. 2019; Dumbili 2020; Dumbili et al. 2021), but the present review was unable to ascertain the mechanism of action of their psychoactivity and thus did not include them among the psychoactive plants reviewed by the present study. The present study perceived the recreational use of the plants as more of satisfying the urge to smoke rather than the need for psychoactivity. Furthermore, the studies never noted that the plants were used for their psychoactive potentials by recreational users.

Conclusion

The present study established the recreational use of *Cannabis sativa*, *Datura stramonium*, *Nicotiana tabacum*, and *Carica papaya* in Nigeria. Their prevalence of recreational use, mechanism of neuroactivity, and neurotoxicity were also reviewed. Interestingly, the present review linked the beliefs of the Nigerian communities to the higher prevalence of psychoactive plants use in the country, compared to the global level. Prevalent of the national beliefs were that the plants' use will foster social belonging and bonding, enhance performance and abilities, and satisfy their desire and curiosity for adventure. This study concludes that all the reviewed plants are toxic at certain doses and prolong exposure, while some users even combine two psychoactive plants or with synthetic psychoactive substances, which will aggravate toxicity more. The present study recommends that the control of the recreational use of these plants in Nigeria should be revamped and overhauled while programs that educate victims regarding the associated hazard should be reinvented to significantly solve the problem. Also, an indigenous nationwide survey of the use of the psychoactive plants is recommended, as most indigenous studies are just a town, city, or region based while international studies will never truly access the communities as the plants cultivation and recreational use attracts consequences which may deter the community dwellers from interacting with international bodies.

Declarations

Ethics approval None.

Consent to participate All the authors contributed substantially to the work, participated in the writing, and have seen and approved the submitted version.

Conflict of interest The authors declare no competing interests.

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