Chapter 17

Psychoactive Drugs

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Chapter Outline

Learning Objectives

- To define and give examples of psychoactive ingredients
- To identify the main plant sources of psychoactive drugs and their points of origin
- To have a comprehensive understanding of *Amanita muscaria*, *Myristica fragrans*, and *Cannabis sativa*; their traditional use; their confirmed biological activities and active ingredients connected to these; their adverse effects

17.1 DEFINITION

Psychoactive drugs in general affect the central nervous system (CNS). Many are obtained from plant material, either in extract form or isolated compounds that can excite and enhance mental alertness and physical activity without altering consciousness; reduce fatigue and hunger (stimulants); while they can also repress mental activity; awareness; physical performance (depressant); and cause changes in mood, space and (or) time perception, visions, illusions (hallucinations).

17.2 EXAMPLES

Hallucinogens occur in different genera of fungi such as *Amanita*, *Psiolcybe*, *Conocybe*, and higher plants. Plants with hallucinogenic properties are present in most botanic families, e.g., wormwood (*Artemesia absinthium*; *Asteraceae*), diviner's sage (*Salvia divinorum*; *Lamiaceae*), deadly nightshade (*Atropa belladonna*; *Solanaceae*), peyote (*Lophophora williamsii*; *Cactaceae*), iboga (*Tabernanthe iboga*; *Apocynaceae*), and many others.

17.3 PLANT SOURCES

17.3.1 Amanita Muscaria

The fly agaric (*Amanita muscaria*) is a poisonous mushroom with a characteristic red or orange cup, often covered with white flecks. Various species occur in many continents and usually grow in deciduous wood, especially beech and birch as well as coniferous ones. In some parts of northeastern and western Siberia, the local tribes (e.g., chuckchee) use the

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fly agaric as an intoxicant. These inhabitants of Siberia ingest the mushroom alone, either sun-dried or toasted slowly over the fire. They may also take it as reindeer milk or with juice of wild plants, like those of a genus Vaccinium. The symptoms start after 20–30 min and usually end within 2 h. A small dose (up to four mushrooms) can cause dizziness, nausea, tiredness, a feeling of weightlessness, visual and auditory hypersensitivity, space distortion, unawareness of time, and colored hallucinations [1]. A larger dose gives more pronounced symptoms of poisoning with spasm and more vivid hallucination. Aggressive attitudes have not been reported. As a result of the poisoning, dryness in the mouth and mydriasis (dilation of the pupils) can occur followed by a period of drowsiness, then a deep sleep with vivid dreams, usually 2 h after. After the deep sleep, which generally lasts 8 h, the poisoning ends [2].

For a long time, it was believed that the intoxicating effects of *A. muscaria* was due to the alkaloid, muscarine (Schmiedeberg O, Koppe R. Das Muscarin, das giftige Alkaloid des Fliegenpilzes (in German). Leipzig, Germany: F.C.W. Vogel. OCLC 6699630;1869), but the concentration of this ingredient is in such minute concentrations (up to 3 mg/kg of fresh mushroom), that it could not act as the inebriant. It is now recognized that, in the drying or extraction of the mushrooms, ibotenic acid forms several derivatives. The most important is muscimole (formed through decarboxylation of ibotenic acid), the main pharmacologically active principle. Other compounds, such as muscazone, are found in lesser concentrations and may contribute to the intoxication. Ibotenic acid (α-amino-3-hydroxy-5-isoazoloacetic acid) as well as muscazone can be regarded as amino acids, while ibotenic acid and muscimole are oxazol derivatives.

Most bioactive ingredient in *Amanita muscaria*: muscimole

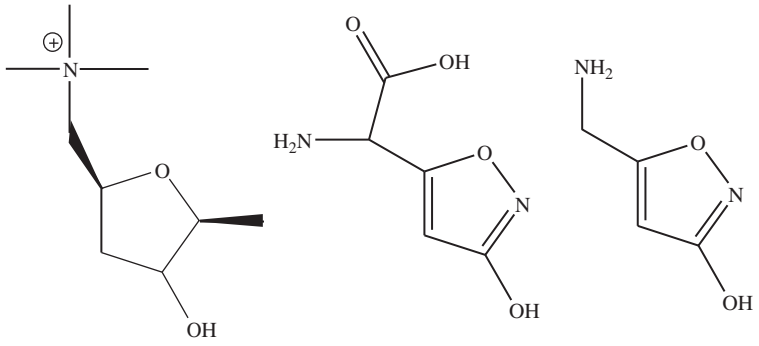
The mushroom is given the name fly agaric because of its age-old use in Europe as a fly killer. The mushrooms were left in an open dish, flies were attracted to and settled on the mushrooms, the flies were subsequently stunned resulting in the mushroom being deemed as having insecticidal properties.

Fly agaric = fly killer, an observation made in Europe years ago

17.3.2 Bioactivity

In vivo research confirms that biochemical changes develop 30 min after peritoneal injection of aqueous extracts of *A. muscaria* into male rats. Such changes included a decrease of acetylcholine esterase activity, liver glycogen, and blood urea nitrogen, together with an increase of blood glucose levels. Serum transaminase activities were not affected and all values returned to normal within 6 h [3]. The latter data demonstrated that the poisoning was not detrimental as vital organs like the liver and kidneys were not affected.

Fig. 17.1 shows the chemical structures of isozasol derivatives (ibotenic acid and muscimol) present in *A. muscaria* which are similar to those of glutamic acid and GABA (γ-aminobutyric acid), products of their enzymatic decarboxylation. Similarities in the structures of these compounds are thought to contribute to their ability to bind and activate receptors of endogenous [4].



(+) Muscarine Ibotenic acid Muscimol

FIGURE 17.1 Psychoactive ingredients: ibotenic acid and muscimol.

Behavioral changes, like ataxia and sedation, induced by muscimol (agonist of $GABA_A$ receptor and partially $GABA_c$ receptor) in mice depend on high-affinity binding of this compound to a distinct subtype of $GABA_A$ receptor in the cerebral cortex [5]. Moreover, mucimol inhibits GABA uptake by neurons and astrocytes and is a substrate to GABA transaminase [4,6,7]. For this reason the structure of muscimol was used as a template for the design of GABA uptake inhibitors and GABA agonists [7].

It is assumed that the two main compounds responsible for the hallucinogenic properties of *A. muscaria* are ibotenic acid and muscimol and the mechanism of their activity is connected to ligation of glutamate and GABA receptors, respectively [4]. However, the studies concerning the connection between brain activity involved with paradoxical sleep appearance and various paradoxical sleep-associated phenomena (called pedunculopontine tegmental nucleus) seem to negate hallucinogenic properties, both GABA and glutamate agonists.

The injection of glutamic acid and muscimol into pedunculopontine tegmental nucleus in rats resulted in induction or suppression of one of the paradoxical sleep hallmarks [8]. Influence of both toxins on the sleep architecture seem to be due to GABA and glutamate-dependent mechanisms that modulate activities of cholinergic neurons within pedunculopontine tegmental nucleus [4,9]. Muscimol, dose-dependently, affected encephalogram in experimental animals clearly differently from other typical hallucinogens such as LSD and mescaline. Particularly, electroencephalogram pattern caused by muscimol showed spikes, characteristic of convulsing activity [4,10]. Injected intravenously, muscimol also potentiates analgesic effects of opiates (morphine) in rats and mice and these effects are disrupted by GABAergic system [11,12].

17.3.3 Adverse Effect

It is important that the intake of fly agaric (*A. muscaria*) does not cause any damage to organs (liver, kidneys) and subsequent gastrointestinal disorders with vomiting are inconstantly reported [13]. Nevertheless the active components of *A. muscaria* may induce in vivo brain lesions. Regular consumption of the mushroom would probably be harmful, even though the vast majority of human poisoning cases do not report any after-effects [1].

17.4 MYRISTICA FRAGRANS

Nutmeg (*Myristicae semen*) is the kernel of the dried, ripe seed of *Myristica fragrans* Houtt, belonging to family Myristicaceae. The nutmeg tree grows to 10−20 m in height, with a natural origin in the Moluccas, but it has been cultivated in Indonesia, Malaysia, Sri Lanka, and the West Indies. *M. fragrans* is a dioecious tree, bushy and evergreen. In plantation the number of male trees is reduced to roughly 10% in total. The fruit is a one-seeded fleshy drupe, yellow and pear-shaped. During fruit ripening, the aromatic, orange pericarp splits, disclosing the black seed surrounded by a red, net-like aril, which is separated and dried to give the crude drug mace. The seed, after removing the red aril is dried in high temperature (in the oven) until the kernel shrinks and rattling can be heard in the testa. Seed shell (testa) is crushed after and separated from the kernel, which is the proper nutmeg drug. Nutmeg contains 30−40% of fats and about 10% of essential oils [14], which is mostly composed of terpenes (α-pinene, camphene, p-cymene, sabinene, β-phellandrene, γ-terpinene, myrcene), terpene derivatives (linalool, geraniol, terpineol), and phenylopropanes (myristicin, elmicin, safrole) [15]. Mace oil has a similar composition, but it contains higher levels of terpenes. Both nutmeg and mace are the two major primary products of *M. fragrans* that are commercially used as spices.

17.4.1 Bioactivity

Various extracts and essential oils of nutmeg seeds have been reported with antimicrobial activities against gram-positive and gram-negative bacteria, as well as a variety of fungi. Ethanolic extract of nutmeg seeds demonstrated antimicrobial activity against enterohemorrhagic *Escherichia coli*, which was found to be highly sensitive to β-pinene [16]. Another research reported potent antibacterial activity of chloroform extracts, against both gram-positive and gram-negative bacteria and trimyristin and myristic acid proved to be the chief antibacterial principles isolated from *M. fragrans* Houtt [17].

The nutmeg extracts demonstrated antifungal activity against *Candida albicans* and *Aspergillus niger*. Earlier studies have proposed that one of the mechanisms of the antifungal effects involved the inhibition of various cellular processes, followed by an increase in plasma membrane permeability and finally ion leakage from the cells [18]. Methanol extract of *M. fragrans* Houtt., containing lignans, has AChE (acetylcholinesterase) inhibition activity. Different AChE

inhibitors have been shown to significantly improve the cognitive function in Alzheimer's disease (these compounds enhance the signal transmission in nerve synapses by prolonging the effect of acetyl choline) [19].

It has been reported that myristicin, present in the volatile oil of *M. fragrans*, is a potential chemopreventive agent, by way of its ability to induce the activity of the detoxifying enzyme system, glutathione *S*-transferase [20]. In addition, extracts of nutmeg strongly suppressed the growth of human lymphoid leukemic cells (Molt 4B) [21]. Moreover, the dihydroguaiaretic acid from *M. fragrans* mace suppressed the viability of several cancer cell lines, leukemic, colon, and lung [22]. Myristicin, as well, induced apoptosis via the mitochondrial pathway and downregulated genes belonging to the DNA damage response pathway in human leukemia cells [23].

In vivo research examined the antimutagenic potential of nutmeg in male wistar rats. The plant extract showed significant bioactivities as there was a decrease in the mutation index in a dose-dependent manner. This was due to the antioxidant activities of the present phytochemicals that scavenged the active oxygen radicals [24].

17.4.2 Adverse Effects

Consumption of nutmeg seeds in large quantities cause a hallucinogenic effect, which is followed by unpleasant side effects such as facial flushing, tachycardia, hypertension, dry mouth, feelings of euphoria, unreality, and delirium. Several cases of nutmeg seed ingestion have been reported in adolescents who attempted to achieve a euphoric state at low cost [25]. For the psychoactivity of nutmeg to be experienced, the metabolic conversion of the two components of nutmeg essential oil, myristicin and elmicin into compounds similar to amphetamine has to take place. As a result of the metabolism of elemicin, 3,4,5- trimethoxyamphetamine is produced and metabolism of myristicin leads to 3-methoxy-4,5-methylenedioxy amphetamine [26]. Moreover, myristicin, as a weak inhibitor of monoamine oxidase, could be responsible for some symptoms of circulatory disorders [27].

17.5 CANNABIS

Cannabis (Indian hemp, *C. sativa* herba) consists of the dried, aerial parts of *C. sativa* L. belonging to family Cannabidaceae (also Cannabaceae). It is an annual diecious, wind-pollinated herb, with male and female flowers that develop on separate plants. The leaves and bracts on both types of plants have unicellular covering hairs with a pointed end and wide base. They also have glandular hairs which secrete a resin rich in cannabinoids. The plant occurs naturally in India, Bangladesh, and Pakistan and is grown in numerous countries with tropical climates suitable for fiber and seed production. The stem of the plant, which can grow up to 10 cm in diameter, contains long and tough fibers (the most durable fibers of natural origin), which are used for the production of ropes, carpets, etc. Although both male and female plants produce cannabinoids, female plants produce larger amounts of the resin and this is the reason they are preferred.

17.5.1 Cannabinoids

Cannabinoids are a group of C_{21} compounds occurring in resin produced by glandular hairs of *C. sativa* L. Among the over 420 known constituents of cannabis, more than 60 belong to cannabinoids, which chemically belong to the terpenophenols. Cannabinoids (phytocannabinoids) are accumulated in the glandular hairs, which account for more than 80% of the subcuticular secretion. Generally, they are present in all plant parts, except the seeds.

There are no qualitative differences in cannabinoid content among particular plant parts, only quantitative. The highest concentration of cannabinoids can be found in the bracts of the flowers and fruits while the other parts of the plant (foliage leaves, stem, and roots) possess lower amounts of the active phytocannabinoids.

The most important representative is Δ^9−tetrahydrocannabinol (THC), which has hallucinogenic properties. The other principal components are: cannabinol (CBN), cannabidiol (CBD), Δ^8−tetrahydrocannabinol, cannabigerol, and cannabichromene (CBC).

Most of the cannabinoids have an acid analog, where the only difference is the presence of a carboxyl group (acidic cannabinoids are regarded as being the primary compounds). In the fresh plant material they may occur in larger amounts compared to their neutral counterparts. The main cannabinoids (THC, CBD, CBN, and CBC) are usually detected in each breeding strain or cultivar of *C. sativa*. For the cannabinoid profile of a plant, storage and breeding conditions play a significant role along with variations during preparations of the medicine, mixing with other components (e.g., tobacco), and heating. Findings confirm that cannabinoids, except those produced from biosynthetic

pathways (acidic cannabinoids), leaving mainly the neutral cannabinoids (the majority that result from decarboxylation) are products of degradation (oxidation and isomerization) and are called artifacts. For example, cannabinoids of the CBN type are not formed as by-products of plant metabolism, but rather oxidative degradation of THC and CBD types. Also the Δ^8−tetrahydrocannabinol is the product of isomerization of THC.

17.5.2 Hallucinogenic Effects of *C. sativa*

The main reason why people almost all over the world use cannabis is to get "high." Cannabis users understand this term, as an experience of euphoria, relaxation, perceptual alternation, and the intensification of ordinary sensory experiences, such as eating, watching films, and listening to music. The "high states" may be accompanied by excessive laughter and talkativeness. Cognitive effects (including short-term memory and feeling of associations), motor skills, and reaction time are impaired. Since cannabis, specifically THC, lowers the psychological inhibitions comparable to alcohol, it may be perceived that sexual impulse and libido are heightened. The perception of senses like touch, smell, hearing, taste, and so on are sharpened and hence the sexual stimulants that lead to sexual arousal can be perceived to be enhanced. For that reason cannabis "products" are also used as aphrodisiacs. Body perception may become distorted after smoking a certain dosage of marijuana as spatial-temporal perception may alter in a dose-dependent manner. Time is perceived to pass slower or sometimes faster.

The tactile perception may become more intense. Visual hallucinations occur, about which the subject is aware that these are the acute effects of THC, not the reality. Hallucinations can appear as bright and colorful light flashes. After the ingestion of cannabis (including as a main compound THC), the following symptoms can occur: lowered skin temperature, increased heart rate and blood pressure, analgesia, sedation, slowed speech, slow reaction time and coordination disorder, challenges with concentration and memory, feelings of extreme pleasure, giggling and laughter, different feelings of senses (music may seem more distinct and subtle colors more brighter), a strong desire for food, impaired time perception, and feeling of being separated from reality. Less frequently occurring symptoms are delusions, seeing and hearing, anxiety, panic, attack of paranoia (feeling of being scared or suspicious without reason). Long-term effects include short-term memory impairment, difficulty in learning and problems solving, breathing problems, reproductive system problems, decreased motivation, and low energy [28−33].

17.5.3 The Endocannabinoid System

Natural cannabinoids (phytocannabinoids) are substances acting on the endocannabinoid system (ECS), which regulates numerous physiological processes. There are two types of cannabinoids' receptors: CB1 and CB2. The CB1 receptors have been shown to be highly concentrated in neuronal cells of the CNS, especially those placed in the cerebral cortex, hippocampus, lateral caudate-putament, substantia nigra pars reticulate, and cerebellum [34,35]. This location explains documented effects of cannabinoids on cognition and brain function. Agonists of CB1 receptors also exhibit analgesic properties reflective of the role presence of CB1 receptors on pain pathways in the brain and spinal cord and at the peripheral axons of primary sensory neurons. CB1 receptors are present at low levels in neurons located in peripheral tissues, including heart, bladder, vascular smooth muscle cells, lung smooth muscle cells, and intestine [36].

Within the CNS, endocannabinoids and their receptors modulate neuronal signaling and play very important roles in the regulation of movement (coordination of motor function, posture, balance), sleep, emotion, appetite, body temperature, memory storage, and pain perception.

The second type of cannabinoid receptors (the CB2 receptor) are found preferentially in the periphery. They are located in the cells of the immune and hematopoietic system, but have been found to also be present in the brain and other tissues. The presence of the CB2 in the lymphoid organs (tonsils, thymus, spleen) is prerequisite, that in addition to their psychoactive effects in the CNS, the ECS has a role in modulating the immune system. Indeed, cannabinoids have profound influence on cell mediated immunity by inhibiting the proliferation of T cells, cytokine secretion (proinflammatory agents), and the humoral responses from B cells. Such bioactivities demonstrate the therapeutic potential of cannabinoids as antiinflammatory agents [37].

The two best studied endogenous agonists of cannabinoid receptors are: anandamide (*N*-arachidonoyloethanolamide) and its glycerol ester 2-AG (2-arachidonoyl glycerol). The former acts as an endogenous ligand for the aCB_1 receptor, but has a very low affinity for the CB_2 receptor. 2-AG exhibits agnostic patterns to both receptors.

17.5.4 Bioactivity

17.5.4.1 Parkinson's Disease

Parkinson's disease (PD) is overwhelmingly a chronic, progressive, and neurodegenerative disease caused by the degeneration of dopamine-containing neurons of the substantia nigra, which innervate the striatum. Termination of dopaminergic neurotransmission subsequently interferes with the function of the basal ganglia decisive to coordination of motor function. Therefore PD characteristic symptoms are bradykinesia (slowness of movement), akinesia (postural immobility), muscular rigidity, resting tremor, and postural instability [37,38].

Several cannabinoid receptors, representing CB_1 type in the basal ganglia suggests that cannabinoids could play a therapeutic role in the treatment of movement disorders associated with PD [37].

In general there are three phases in PD development:

1. Early presymptomatic phase characterized by neuronal malfunctioning rather than neuronal damage (death), associated with downregulation or desensitization of CB_1 receptors [39,40].
2. Intermediate and advanced symptomatic phase, when the most important process is neuronal death. The PD characteristic is upregulation of CB_1 receptors, which is caused by adaptive responses and is also compatible with the akinetic profile of these patients [40,41]
3. The presence of CB_2, receptors that are characteristic of immune function, as basal ganglia structures show activation of glial elements during pathological processes. The activation of astrocytes and microglia, linked to neuronal injury in lesioned structures in PD is associated with upregulatory responses of CB_2 receptors that are located in cells, which play a role in the protection of neurons [40,42].

Different experimental models of PD exhibit elevated levels of activity of the ECS as the basal ganglia is increased. Such elevated activity is manifested by increased CB_1 activity, anandamide (endocannabinoid) levels, and decreased cannabinoid clearance [43]. Despite the upregulation of the CB system that is noticed at intermediate−late stages of the disease process, in the earlier, presymptomatic phase of PD, CB_1 receptors are desensitized, which may render the basal ganglia more vulnerable to the cytotoxic environment of the cranial activity associated with PD, which promotes excitotoxity according to the loss of CB_1-mediated presynaptic inhibition of glutamate release [44,45]. As a result of their ability to inhibit glutamate release and so mitigate glutamate-mediated toxicity, cannabinoids may prove useful as potential therapeutic targets against PD [34]. Given the fact that CB receptors promote hypokinesia, antagonists of the CB_1 receptors confirmed by preclinical studies should be likely potentials for the treatment of PD in order to counteract the consequences of an upregulation of the cannabinoid system that is common at the advanced stage of the disease.

Despite the undesired effects of the hypokinetic profiles of CB agonists (some phytocannabinoids (Fernández-Ruiz J. The endocannabinoid system as a target for the treatment of motor dysfunction. Br J Pharmacol. 2009;156:1029−40), some have shown neuroprotective properties which would aid in halting the neurodegenerative aspect of the disease. Preclinical studies have indicated that cannabinoids may attenuate neurodegeneration in animal models with PD. This is believed to be attributed to the antioxidative action of THC and CBD responsible for the neuroprotection observed against 6-hydroxydopamine, an inducer of neurotoxicty in the animal models [46]. Further, THC exhibited neuroprotective effects toward human neuroblastoma cells exposed to several PD-relevant toxins, however, neuroprotection was not blocked by CB_1 receptor antagonists [47].

Although many cannabinoids demonstrate neuroprotective effects in several models of PD where effects appear to be mediated by a CB-receptor-dependent mechanism, the same is also true for CB-independent mechanisms. This includes antioxidant effects, reduced microglia activation, and modulation of glial−neuron interactions [45]. Phytocannabinoids are capable of reducing oxidative damage by acting as scavengers of reactive oxygen species (ROS) and by enhancing endogenous antioxidant defenses [46].

Observational and uncontrolled studies suggest that cannabinoids may improve motor symptoms associated with PD. A survey was conducted in the Czech Republic to investigate the use of Cannabis and its effects on PD so patients who suffered with PD were examined. Findings indicated that 25% of the respondents reported using cannabis and 46% of them noticed some benefits; 31% reported improvement of rest tremor; 45% reported improvement of bradykinesia; and 14% reported improvements of Levodopa-induced dyskinesia [48]. Improvements in rigidity, tremor, bradykinesia, and pain were also reported in another, small ($N = 22$) open-label trial that assessed motor symptoms 30 min after smoking cannabis [49].

17.5.4.2 Cancer

Numerous recent studies have linked associations between cannabinoids and cancer. Firstly, the role of cannabinoids or cannabis smoking to cancer initiation and/or development; secondly, the role of cannabinoids as potential anticancer therapies; and lastly, the role of cannabis and cannabinoids in the palliation of common cancer-associated symptoms [50].

One of the primary concerns associated with the medical use of cannabinoids, especially inhaled cannabis, is their carcinogenic potential. Most of the studies that have investigated a connection between marijuana smoking and cancer have been case-controlled in which patients with cancer were compared with persons without the disease. Noteworthy is that tobacco smoking was found to be an important confounder [51]. Although one case−control study showed a link between marijuana smoking and incidence of head and neck cancer [52]. For lung cancer, a case−control study found no connection with marijuana smoking (even for those smokers who used more than one marijuana cigarette per day for 30 years) after adjustment for confounders (tobacco smoking) [53].

A systematic review, concerning a correlation of lung cancer and cannabis smoking, evaluating 19 studies from 1966 to 2006 have not confirmed associations among cannabis smoking and lung cancer development despite clear evidence of precancerous histopathologic changes of respiratory mucosa [50,54]. One study found no increased risk of lung, colorectal, melanoma, or breast cancers in current and former smokers of marijuana versus never smokers or experimenters (very rare use of cannabis) [55]. This could be due to the in vitro effect of THC and other cannabinoids on cell metabolism, DNA synthesis, and cell division, events that halt cell division rather than lead to cancer [56].

Research has shown that THC and other phytocannabinoids are mutagenic in standard microbial assays though such findings warrant further investigations [57]. There are no published studies addressing oral marijuana ingestion and vaporized ingestion to cancer risk.

17.5.4.3 Anticancer Effects of Cannabinoids

Evidence suggests that THC, naturally occurring cannabinoids (e.g., CBD, CBN), synthetic cannabinoid agonists, as well as endocannabinoids exhibit antineoplastic effects in vitro against lung carcinoma, gliomas, lymphomas, skin carcinomas, uterine carcinoma, and neublastoma [58].

Other studies have demonstrated in vitro and in vivo tumor growth inhibition of glioblastoma multiforme, breast, prostate, thyroid, colon, skin, pancreatic, leukemia, and lymphoma models [59]. The antitumor effects of these phytochemicals was found to occur via the suppression of proliferative cell signaling pathways, the inhibition of angiogenesis and cell migration, the stimulation of programmed cell death (apoptosis), and/or induction of autophagy [50]. For example, in gliomas, the use of THC (natural agonist cannabinoids receptors) induced cell death by downregulating the P13K/Akt and MAPK-signaling pathways that induced apoptosis through the activation of pro-apoptotic Bcl-2-associated death promoter protein [60]. Colon cancer cells exposed to phytocannabinoids experienced tumor necrosis factor-α-mediated, ceramide-induced apoptosis in vivo and in vitro [61]. Apoptosis was induced through ceramide by THC (2 μM and 15 mg/kg/d) in pancreatic tumor cells (Panc 1 and MiaPaCa2) [62]. Additionally decreased expression of the vascular endothelial growth factor one the most important proangiogenic factors was observed in glioma and skin cancer models treated with CB2 receptor selective agonist [63]. Cannabinoid agonists also directly inhibited angiogenesis induced by basic fibroblast growth factor in vitro and in vivo in a CB1-dependent manner [64].

Interestingly, the anticancer activity of CBD is probably completely independent of cannabinoid receptor activation. In bladder, CBD induced apoptosis of cancer cells via the activation of the TRPV2 channel protein, whereas CBD induced apoptosis in breast cancer cells independent of both cannabinoid and vanillin receptors [65,66]. Cannabinoid receptors have been found in higher concentrations in tumor cells than in corresponding normal tissue with variations from cancer to cancer. A good example of this fact is that CB2 receptors are expressed in 91% of HER2-positive breast cancers, in 35−72% of HER2-negative breast cancers, and only in 5% of normal breast tissue [50,67]. In addition to cannabinoid agonists, inhibitors of endocannabinoid transport or degradation have been shown to inhibit tumor growth and progression in numerous types of cancers, enhancing the levels of endocannabinoids in the cells [68].

Also, cannabinoids can selectively cause inhibition in the growth of tumor cells while ideally not affecting healthy tissue. A good example is that glioma cells that were exposed to cannabinoids underwent apoptosis (ceramide-induced) while astrocytes were protected from oxidative stress by the same cannabinoids [50,69].

Although the use of cannabinoids-related drugs for medicinal purposes could be limited by concerns of their psychotropic effects, they have shown to exhibit a reasonable safety profile, especially in comparison to current chemotherapeutics which all have more or less serious toxic adverse effects.

Despite the numerous collected evidence on the therapeutic potential of cannabinoids and related drugs in several types of cancers, only a single pilot clinical study has been performed thus far. This phase I/II clinical trial was aimed at evaluating the safety profile of THC administration and its antitumor activity in a cohort of nine terminally ill patients affected by recurrent glioblastoma multiforme, an aggressive primary brain tumor with poor prognosis (6–12 months survival) and no efficacious treatment. THC decreased tumor cell proliferation, and also induced apoptosis; however, it had only a slight impact on the overall median survival of the cohort (24 weeks) [59,69].

17.5.4.4 Cannabinoids in Cancer Therapy as Palliative Agents

The cannabinoids are emerging as valuable adjunctive agents for optimizing the management of multiple symptoms of cancer and the treatment of therapy-related side effects. In fact, while much remains unknown about the pathophysiological mechanisms of the ECS, available data support a broad spectrum of palliative properties, including appetite stimulation, inhibition of nausea and emesis associated with chemotherapy or radiotherapy, pain relief, mood amelioration, and relief from insomnia [59,70].

In the United States, two medicinal cannabis products (approved by FDA) are available: Marinol, a synthetic form of THC, and Cesamet, a synthetic THC analog. Both are currently approved for chemotherapy-induced nausea and vomiting (CINV) in patients who have failed to respond adequately to conventional antiemetic compounds. Dronabinol (synthetic THC; Marinol) is also approved for the treatment of anorexia associated with AIDS. A third medicinal cannabis product, Sativex (a combination of THC and CBD isolated from *C. sativa* in ratio 1:1) is already approved and marketed in Canada as an adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis [71].

One of the earliest recognized medical indication for cannabinoids was CINV. Approximately one-half of cancer patients will suffer from these side effects of cancer treatment. This may lead to discontinuation of therapy because of noncompliance. To address this problem, antiemetic drugs are routinely given before and after chemotherapy. There is evidence that cannabinoids act on CB1 receptors in the dorsal–vagal complex of the brainstem region controlling the vomiting reflex, and that endocannabinoids and their inactivating enzymes are present in the gastrointestinal tract and might have a physiological role in the control of emesis [59].

Dronabinol and prochlorperazine were tested alone and in combination in a randomized, double-blind, parallel-group, multicenter study. The results of the study showed that a combination was significantly more effective than was either single agent in controlling CINV [72]. Another experiment confirmed a significant increase in appetite and a decrease in nausea in most patients after treatment with dronabinol [73].

Using THC, synthetic cannabinoids, and smoking cannabis, numerous clinical trials showed that the antiemetic effectiveness of cannabinoids is almost same to that of conventional antiemetics, such as dopamine D2-receptor antagonists, 5-HT3 receptor antagonist, and NK1 receptor antagonists [70]. Currently, the efficacy of cannabinoids as first-line treatment is challenging because of the psychoactive aspects and risk for emergence of dependency and tolerance even though they have the potential to target chemotherapy or radiotherapy-induced nausea and vomiting. Therefore, it is considered as second-line treatment in intractable cases and also can be coadministered with other first-line pharmacotherapeutic agents (such as 5-HT3 receptor antagonist) for additive or synergistic effects [74].

Other serious challenges associated with cancer are anorexia and cachexia, the cancer anorexia–cachexia syndrome is an important risk factor for morbidity and mortality in people with cancer. Numerous studies confirmed that THC and other cannabinoids have a stimulatory effect on appetite and increase food intake in animals [75]. The orexigenic effect (appetite stimulation) occurs through the inhibition of leptin at the hypothalamic level [76], because endocannabinoids in the hypothalamus may tonically activate CB1 receptors to maintain food intake. Anecdotal information from cannabis smokers and numerous clinical trials support the appetite-stimulating properties of THC. In fact, the synthetic cannabinoid dronabinol is approved by the FDA for treatment of anorexia associated with weight loss in AIDS patients.

17.5.5 Adverse Effects

Many of the beneficial (for therapy of different diseases) effects of cannabinoids rely on CB_1 receptor-mediated mechanisms (sometimes CB_2 or receptor-independent mechanism too). The high expression of CB_1 receptors in the CNS, like cerebellum and hippocampus, means that therapeutic doses of phytocannabinoids are causing often unwanted effects. Volunteers intoxicated with Δ^9-THC exhibited 3D inversion illusion, which has similarities to a neuropsychological cognitive impairment in the regulation of perception seen in patients with schizophrenia [77]. Some of the more

common adverse effects of phytocannabinoid administration are sedation (result of CNS depression), perception disorders, motor function disorders (like ataxia, incoordination), deficit in short-term memory (cognition disorders), and psychosis [78–80].

In cases where cannabinoids have been used in clinical trials for nausea and vomiting caused by chemotherapy, the most common adverse effects were somnolence, dry mouth, ataxia, dizziness, and dysphoria [81]. Despite the presence of adverse effects from cannabinoids that are usually acceptable in comparison with those caused by other drugs.

Like other intoxicants, marijuana can impair driving skills and increase the risk of motor vehicle accidents as well as accidents caused by the use of dangerous equipment at the workplace (e.g., used during construction work) [82]. Some studies showed that women who used marijuana during pregnancy were more likely to have a still birth [83]. The frequent use marijuana during pregnancy has also been linked to adverse neurobehavioral effects in the offspring [84].

Long-term effects of the administration of cannabinoids include disorders of the respiratory system (bronchitis), cardiovascular system (tachycardia, postural hypotension, aggravation of heart disease), and reproductive system (decreased sperm counts) [37,80]. Marijuana smoking can cause injuries in the large airways and increase the symptoms of chronic bronchitis. However, these effects cease after discontinuing the use of marijuana and there is no clear evidence for connections between marijuana smoking and development of chronic obstructive pulmonary disease [51].

17.6 CONCLUSIONS

Hallucinogenic plants have been used by mankind for thousands of years. Different species with hallucinogenic properties were and still are an important part of culture and religion of primitive tribes as well as well-developed civilizations. Later, hallucinogens have become a part of popular culture and serve as illegal and often dangerous entertainment. Their extensive use as stimulants cause many social problems and an interest in the world of science, firstly because of their adverse effects. Numerous experiments have demonstrated that the active ingredients of hallucinogenic plants, like THC, have different activities and most of them can be used in therapies against major diseases of concern, such as cancer, PD, AD, and sclerosis multiplex. Their influence on the human organism and especially the CNS provides an avenue for further exploration towards the creation of new promising drugs.

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