14 Plants with Anti-Addictive Potential

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Abstract

Drug addiction is prevalent among individuals of modern society, being a major cause of disability and premature loss of life. Although the drug addiction have profound social, economical and health impact in the world population, its management remains a challenge as available pharmacological treatments remains ineffective for most people. The limited efficacy and adverse effects have led to a search for alternative therapies to treat drug addiction. In this context, natural products are an important source for new chemical substances with a potential therapeutic applicability. Therefore, this chapter will present data obtained after an extensive literature search regarding the use of medicinal plants as a pharmacological alternative for drug addiction treatment.

Keywords

Addiction · Drug dependence · Natural products · Substance abuse · Opioid dependence

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14.1 Introduction

Drug addiction is one of the leading causes of disability and premature death worldwide, being accompanied by high costs for the world economy, mainly on health care, law enforcement, lost work productivity and other direct and indirect costs [140]. According to the World Drug Report, published by United Nations Office on Drugs and Crime in 2019, 35 million people suffer from drug use disorders and require treatment services in the world. This number increased in comparison with the previous estimate, which was of 30.5 million. In 2017, 585,000 people died as a result of drug use. The most commonly used drug is Cannabis, corresponding to 3.8% of

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the global population aged 15–64, followed by opioids, amphetamines, ecstasy and cocaine [175].

Drug addiction is understood as a chronic relapsing mental disorder characterized by compulsive drug-seeking, loss of control in limiting drug-intake and a negative emotional state when the access to the drug is not allowed. This process is strongly associated with genetic, neurodevelopmental and sociocultural factors [92]. Clinically, the diagnosis criteria for drug addiction/substance-use disorder is established by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5). In overall, the diagnosis is based on a pathological pattern of behaviors related to the use of the substance [199]. According to DSM-5, the substance use disorder presents on a range from mild to moderate to severe, with severity of an addiction depending on how many of the established criteria are applied [9, 92].

It is widely accepted that most abuse drugs produce their initial reinforcing effects through the activation of brain reward circuits. Chronic drug use impairs brain function, interfering with the ability of self-control over drug-taking behaviors and making the brain more sensitive to stress and negative moods [184]. Dopaminergic neurons located in the midbrain ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAc) play a key role in the processing of reward-related stimuli. Drugs with addiction potential, through their action in different molecular targets, increase the dopamine release in the NAc and thus the mechanism through which the brain signals reward [133, 184, 185].

Substance use disorders are chronic conditions that often require long-term management (National Institute on Drug Abuse). At present, the pharmacological treatment for drug addiction primarily targets the specific action site of each drug. For example, the most recommended treatment for opioid-use disorder is opioid partial or full agonists, buprenorphine and methadone, respectively. Another example is the treatment of nicotine addiction by modulating the activity of nicotine receptors [105]. However, to date, there are no medications to specifically treat many drug use disorders, such as those caused by cannabis and stimulants [175]. Furthermore, it is important to mention that many current treatments produce serious side effects [105]. Although drug addiction have profound social, economical and health impacts in the world community, available pharmacological treatments are ineffective for most people [133]. The limited efficacy and adverse effects calls for the search for innovative drug addiction therapies, as recommended by the National Institute on Drug Abuse (NIDA). There is a clear need to develop better treatment strategies that find the biological substrates of addiction across stages, including detoxification, recovery maintenance, and relapse prevention [132].

In this context, natural products can be an important source for new chemical substances with potential therapeutic applicability [28, 108]. About 35% of the 1.1 trillion US dollars annual global medicine market originated directly or indirectly from natural products including plants (25%). With the development of cutting edge technology for chemical analysis and plant propagation natural-derived products constitute an extremely important resource for research and development strategies among global pharmaceutical companies. There are many examples of plant-derived extracts and/or compounds isolated from plants that have been widely used in the treatment of many significant diseases [19]. In addition, most classes of drugs have a substance of plant origin as a prototype molecule, demonstrating the importance and usefulness of studying natural compounds [52].

Among the strategies for the search for new pharmacologically active molecules from plant origin is ethnopharmacology, in which the therapeutic properties alleged by users and specialists of traditional medicine systems for homemade medicinal practices are examined, especially herbal preparations [49]. The herbal medicine, that sometimes is also called as traditional or natural medicine, existed in one way or another in different cultures/civilizations, such as Egyptians, Western, Chinese, Kampo (Japan) and

Greco-Arab or Unani/Tibb (south Asia) [52]. It is believed that about 80% of the population worldwide, especially Asian and African countries use plants and herbal medicines as a source for medicinal agents and primary health care. Traditional medicine is an important form of health care for many people and covers a wide variety of therapies and practices, which vary from country to country [35]. Some traditional medicine systems use plant treatments in the management of drug addiction, as for instance documented in traditional Chinese medicine [125, 166]. Although less common, in the west reports of popular use of plants to treat addiction to alcohol and other drugs are also available and scientific publications indicating plants or its products as potentially useful to cope with drug addiction are increasing.

The ethnopharmacology approach includes a valuable shortcut in drug development, since the traditional use by human communities may be regarded not only as indication of effectiveness, but also of bioavailability and acceptable acute toxicity. Ethnopharmacology seems to be particularly useful in diseases without a clear understanding of the pathophysiological substrates when rational drug design is impossible due to lack of defined drug target, as in the case of drug addiction. Another strategy that can be used to investigate products of plan origin is chemotaxonomy, based on the observation that the occurrence of certain chemical compounds is restricted to certain groups of plants. Chemotaxonomy can represent a set of data of great validity in the medical and pharmaceutical fields, which combined with ethnopharmacology, can facilitated the discovery of new drugs of plant origin [57]. The search for derivatives or structurally similar substances due to the chemotaxonomic proximity of a species traditionally used for a given purpose is an example of the combination of ethnopharmacology and chemotaxonomy [47]. Therefore, giving this context, this chapter will present and discuss data obtained after an extensive literature search regarding the use of medicinal plants as a pharmacological alternative for drug addiction treatment.

14.2 Plants Containing Alkaloids as Active Constituents

Alkaloids constitute a large and diverse group of nitrogen-containing secondary metabolites, displaying numerous important pharmacological and physiological effects on vertebrates. Typically, these low molecular weight, heterocyclic compounds exhibit a limited distribution in nature and are called plant toxins due to fact they exert protective effects in plants, acting as a protective chemical strategy against predators and pathogens. Due to their potent biological activities, a number of alkaloids are medicinal agents of inestimable therapeutic status in current clinical use, such as the hypnoanalgesics morphine and codeine, obtained from opium poppy plants (*Papaver somniferum*), the anti-cancer vincristine from periwinkle (*Catharanthus roseus*) and the sedative scopolamine isolated from Solanaceae species. Other well-known alkaloids include the psychostimulant agent caffeine, present in daily beverages, nicotine in tobacco, and cocaine, used for both medicinal and recreational purposes, obtained from leaves of *Erythroxylum* species growing in South America. Although a number of medicinal plants containing promising bioactive alkaloids are still used only in folk medicine, many species are supplied to pharmaceutical industries to produce extracts and derived herbal medicines end-products. Important examples are goldenseal (*Hydratis canadensis*), source of berberine and used to reduce symptoms of cold, flu and sore throat, and boldo (*Peumus boldus*), frequently used in phytomedicines to relieve digestive complaints. Considering their modulatory effects on CNS, many alkaloids are also called neuroactive molecules, binding and interacting to specific receptors due to the presence of a nitrogen-containing core, which resembles the structure of neurotransmitters (for further readings, see [118]).

14.2.1 *Mitragyna speciosa (Korth.)* Havil (Rubiaceae)

Kratom is the common name of a medicinal plant native to Southeast Asia (*Mitragyna speciosa*) and cultivated in Myanmar, traditionally used by

local communities in Thailand and Malaysia as a mood enhancer to increase work performance. The fresh leaves of kratom tree are typically chewed or smoked, used in herbal decoctions or even swallowed when dried and ground leaves are incorporated into beverages and food to masker their bitter taste [124]. Cultural and recreational uses are associated to their putative opioid and non-opioid effects, producing stimulant effects similar to classical opioids. Early reports claimed that heavy users of kratom could undergo intense fatigue situations even under extreme hot weather. Side effects in kratom consumers are reportedly less severe compared to the effects of poppy opioids, undergoing less mental and physical impairment disconnected to the stigma associated to opioid abuse. Several monoterpene indole alkaloids, sharing a corynanthe-type core are described in *Mitragyna speciosa*, being mitragynine (Fig. 14.1a) and 7-hydroxymitragynine (Fig. 14.1b) the main bioactive compounds [4]. In terms of concentration, mitragynine is the major alkaloid in kratom, present in higher quantities in leaves collected in Thailand (66%) than in those collected in Malaysia (12%). Although the kratom alkaloids do not share the structure of morphine and other opioid analgesics, mitragynine and their analogues produce euphoria, induce sexual desire and stimulation effects, being a sedative-narcotic at higher concentrations [11, 177, 188]. Prolonged use of kratom preparations is associated with tremors, convulsions and psychosis symptoms. Such effects are associated to its potent full agonist activity on μ and κ opioid receptors, 13 times more potent than morphine [117]. Additionally, 5-HT_{2a} and postsynaptic α2-adrenergic receptors as well as neuronal calcium-channels blocking are associated to the pharmacological activity of mitragynine [116]. Due to their alleged addictive properties, kratom is tested in non-medically supervised treatment of opioid abstinence syndrome [187]. Currently, kratom use is prohibited in Malaysia and criminalized in Thailand. In U.S., it is considered a legal opioid replacement of easy obtainment in some states, despite the fact that its use remains unregulated by FDA. Preclinical investigations conducted with *Mytragina speciosa* aqueous extracts demonstrated a remission on withdrawal symptoms following the cessation of chronic alcohol consumption in mice and the reduction of jumping behavior induced by naloxone in rodents on a morphine withdrawal syndrome model [29, 183, 196]. However, a number of case reports detail abuse potential and important side effects including seizures and hepatotoxicity in kratom users. In 2017, the U.S. Centers for Disease Control and Protection (CDC) notified 152 deaths involving the use of kratom, especially prevalent in heroin and fentanyl users who co-administer this drug along with other opioids [182]. To date, no scientific evidences demonstrating the safe use of kratom in opioid-dependent patients to reduce morphine intake have been found in scientific literature. As such, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) controls *Mitragyna speciosa* and mitragynine both sell and usage in a number of E.U. countries. Neither *Mitragyna speciosa* nor mitragynine or other kratom alkaloids are currently listed in any of the

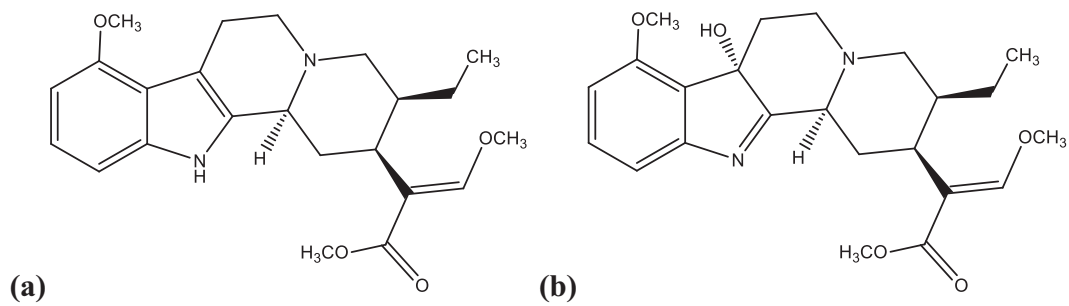


Fig. 14.1 Structures of the bioactive kratom alkaloids: (**a**) mitragynine and (**b**) 7-hydroxymitragynine

Schedules of the United Nations Drug Conventions [4].

14.2.2 *Tabernanthe iboga* Baill. (Apocynaceae)

The iboga plant (*Tabernanthe iboga*) is a shrub native to West Africa, found in Gabon and Cameroon, traditionally used in rituals of the Bwiti religion by shamans who are said to detain the knowledge about the psychoactive properties of the plant. Their ceremonies involve the preparation of a potion made with root barks of *Tabernanthe iboga*, which can be used in infusions or also be chewed [76]. In a religious context, the ingestion of the preparations in higher doses produce the characteristic psychoactive effects, including hallucinations and the power to connect with spirits of the ancestors in rites of passage [34]. The root barks of iboga contain a number of different indole monoterpene alkaloids, which includes ibogaine, ibogamine and tabernanthine. Among these, ibogaine (Fig. 14.2a) is the major alkaloid in plant material and herbal preparations, found in concentrations up to 80% and being considered the bioactive compound of iboga. The pharmacological properties of ibogaine include psychedelic, hallucinogen and oneirogenic effects, leading to a waking or lucid dream state of consciousness. The mechanism of action for both ibogaine and its metabolite noribogaine (*O*-desmethylibogaine) is complex, acting as antagonist on NMDA glutamate and α3β4 nicotinic receptors, agonist on κ- opioid receptor and 5-HT_2, 5-HT_3 [97, 111]. On μ-opioid receptors, ibogaine behaves as a weak or partial agonist [200]. The modulation of opioids receptors is connected to the psychoactive effects, while the hallucinogenic effects seem to be connected to the serotonin $5HT_{2A}$ receptor weak agonist modulation [64]. Ibogaine has been used since 1960s in non-medical detoxification settings as an anti-craving agent, reducing the nicotine, cocaine, alcohol, methamphetamine and opioids dependence. This alkaloid was found to decrease accumbal dopamine release and morphine-induced increases of dopamine extracellular levels in the nucleus accumbens, consistent with a putative anti-addictive action [55]. Several preclinical trials conducted in animal models showed reductions in withdrawal signs in morphine-dependent animals, on drug-induced conditioned place preference (CPP) paradigms and on self-drug administration for morphine, alcohol, amphetamines, nicotine and cocaine [8, 25, 54, 154]. Additionally, ibogaine seems to cause a potential reduction in the amount of drug self-administration in animals in a strong and long-lasting manner. Noteworthy, the metabolite noribogaine has about a ten-fold higher affinity for the serotonin transporter than the precursor ibogaine and consistently, noribogaine is more potent than ibogaine in raising extracellular levels of serotonin in the nucleus accumbens [13, 115]. The negative effects connected to ibogaine administration in rodents include impaired motor function and cerebellar Purkinje cell loss in high dosages intraparenterally administered [190]. The efficacy of ibogaine as an alternative for the treatment of opioid addiction has been extensively discussed due to the morbidity and mortality observed with the exponential current consume of illicit drugs worldwide. The administration of low ibogaine doses associated with narcotic painkillers was already proposed for pain management, in order to reduce the use of opioids such as oxycodone. Due to the illegality of ibogaine as a medi-

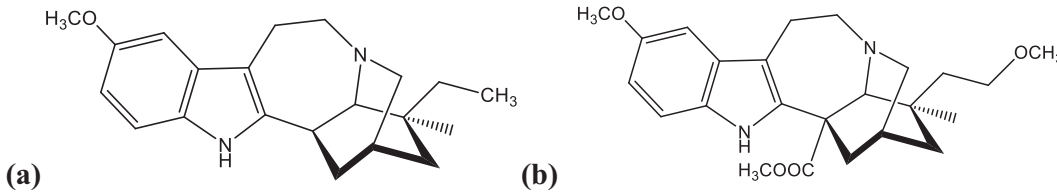


Fig. 14.2 Structures of the iboga-related compounds: (**a**) ibogaine, (**b**) 18-methoxycoronaridine

cal treatment, clinics offering non-regulated applications of the compound for the treatment of opioids craving are spread in many countries, offered in clandestine scene and causing many fatalities. The main reasons rely on the potentially fatal cardiac arrhythmias, tremors, toxicity and acute depressant effect on responding for water observed in pre-clinical assays following ibogaine administration [91]. As such, synthetic 18-methoxycoronaridine (18-MC, Fig. 14.2b) emerged as a derivative to ibogaine with a similar activity on opioid withdrawal signs, decreasing the intravenous self-administration of morphine and cocaine and the oral self-administration of ethanol and nicotine in rats [122, 138, 156]. These alkaloids have similar affinities for μ-and κ-opioid receptors and for 5-HT_3 receptors, attenuating the amphetamine-induced euphoria in humans and cocaine-induced locomotion, alcohol intake, and morphine withdrawal signs in rodents. Conversely, due to the lower affinity for sigma-receptors, fewer side effects are associated to the use of 18-MC, including the neurotoxicity evoked by ibogaine use.

Iboga and ibogaine use for drug addiction remains illegal in several countries, where these substances are used without quality control or a close monitoring of a qualified medical staff. In U.S., FDA declined additional studies with ibogaine due to death reports following an approved clinical trial in humans in 1993. Because of the banned status for ibogaine, 18-MC is supported as an alternative for opioids addiction, with several controlled clinical trial conducted worldwide. Additionally, *Tabernanthe iboga* and ibogaine were added to the list of controlled substances in France and is scheduled in nine countries in the European Union. In other countries, ibogaine is unregulated, except for Brazil, New Zealand, and South Africa where it is regulated as a medicinal substance for use by licensed medical practitioners [34]. Some clinical trials supervised by physicians and accompanied by psychotherapy suggest ibogaine as a safe and effective treatment for dependence on non-opiate users, including alcohol, cannabis, cocaine and crack. Prolonged periods of abstinence without complications or fatalities were observed, and some authors suggest oral and low dosages of ibogaine to minimize heart arrhythmias and deaths.

14.2.3 *Areca catechu* L. (Arecaceae)

Areca nuts are used in the composition of betel quid, a popular herbal masticatory in Asia Southeastern countries, mainly due to its psychoactive properties. Chewing betel nuts is also considered a more socially accepted habit than the use of other types of drugs, causing a perception of well-being, hot sensation in the body and an increased capacity for work [143]. Currently, areca nuts are considered the fourth most popular mind-altering product used worldwide, after nicotine, alcohol and caffeine. However, the prolonged consume may cause addiction and is associated to a number of systemic effects, such as an increased risk of oral cancers, heart attack and other conditions [58]. Arecoline, arecaidine, guvacoline and guvacine are pyridine-type alkaloids found in betel nuts, for which the addictive and carcinogenic effects are attributed. Arecoline is the major alkaloid, able to rapidly cross the blood-brain barrier and exert cholinomimetic effects. In brain, both arecoline and guvacoline behave as muscarinic agonists on acetylcholine receptors, but only arecoline active nicotinic receptors, acting as a competitive inhibitor of gamma-aminobutyric acid (GABA) neurotransmitter, thus causing parasympathetic symptoms as euphoria, salivation and agitation [68]. Withdrawal symptoms are also observed in Areca chewers, including mood swings, anxiety and insomnia [104]. Additionally, hydrolysis of arecoline (Fig. 14.3a) and guvacoline (Fig. 14.3b) produces arecaidine (Fig. 14.3c) and guvacine (Fig. 14.3d), respectively, which are inhibitors of GABA uptake [53].

Some previous studies conducted with a dichloromethane fraction of Areca nuts indicated a reduction on withdrawal symptoms and decrease the number of jumping of naloxone-precipitated morphine withdrawal in mice [94]. The mechanism of action proposed *in vivo* and *in vitro* was a MAO-A inhibitory effect similarly to moclobemide, thus promoting antidepressant

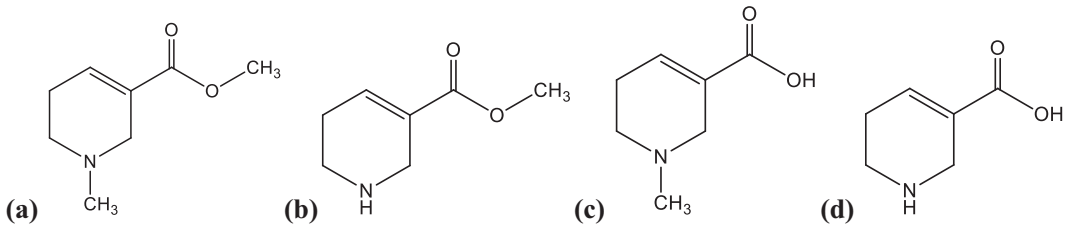


Fig. 14.3 Structures of the Areca compounds: (**a**) arecoline, (**b**) guvacoline, (**c**) arecaidine, and (**d**) guvacine

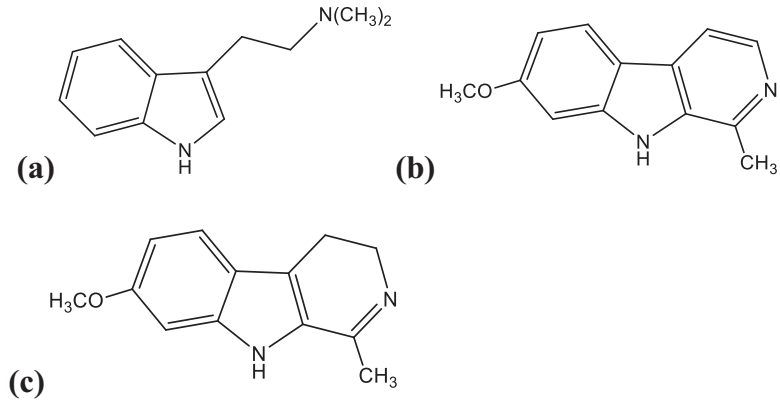


Fig. 14.4 Structures of the ahayuasca alkaloids: (**a**) DMT, (**b**) harmine and (**c**) harmaline

activity. Because Areca alkaloids were not found to inhibit MAO-A, some authors attribute this effect to unknown phenolic compounds present in plant extract.

14.2.4 Ayahuasca - *Psychotria viridis* Ruiz & Pav. (Rubiaceae) and *Banisteriopsis caapi* (Spruce ex Griseb.) C.V. Morton (Malpighiaceae)

The ayahuasca consists of a hallucinogenic brew prepared as a decoction of a mix containing several medicinal plant species, traditionally consumed by Northwestern Amazonian tribes from Brazil, Colombia, Ecuador and Peru due to their healing and spiritual purposes. After oral ingestion, religious leaders and shamans are said to facilitate healing, prophesy, and divination, which spread the use of ayahuasca in ritual ceremonies from syncretic religions as Santo Daime. Among the plant species used for the preparation, stems of *Banisteriopsis caapi* and leaves of *Psychotria viridis* are the main components, which may also include Solanaceae plants as *Brugmansia* sp. and tobacco [123]. *P. viridis* leaves are rich in indole alkaloids, including the psychoactive *N,N*-dimethyltryptamine (DMT, Fig.14.4a), a tryptamine derivative that induces a rapidly altered state of consciousness when smoked or snorted. *B. caapi* is a jungle vine containing β-carboline alkaloids such as harmine (Fig. 14.4b) and harmaline (Fig. 14.4c), all of them reversible monoamine oxidase-A inhibitors (IMAO-A) [102]. DMT is a serotonergic agonist, especially for 5-$HT_{1A/2A/2C}$ receptors, but is inactivate when orally administered due to peripheral (gastrointestinal and liver) metabolism by MAO-A. However, the combination of both species produces pharmacological responses due to the synergic effect, caused by the enzymatic inhibition of MAO by harmane alkaloids, thus preserving the DMT structure. Following the ingestion, the psychoactive effects of ayahuasca typically last six to 12 h, promoting symptoms that may include nausea and diarrhea, intensification of emotions, introspection, positive mood and sense

of well-being [157]. Long-term consumption of ayahuasca may induce alteration in brain cortex thickness, but cognitive or psychiatric disorders were not described. Culturally, members from religious groups incorporating ayahuasca in their rituals report loss of interest in typical use of addictive drugs, including cocaine, barbiturates, amphetamines, solvents, tobacco and alcohol, suggesting the intake of the brew and its alkaloids as anti-addictive agents [28, 48]. Animal models and preliminary clinical evidences suggest the use of these alkaloids for major depression, anxiety and addiction treatment. Results confirmed that DMT and β-carbolines present in ayahuasca showed antidepressive and anxiolytic effects in both humans and animals, due to the serotonergic receptor agonist effects, besides the MAO inhibitory activity [62]. After ingestion in healthy volunteers, ayahuasca also promoted an increase of plasma cortisol levels, which are altered in patients with major depression [45].

A number of anecdotal reports from psychotherapeutic centers using both the brew or ayahuasca alkaloids in the treatment of drug dependence indicate promising beneficial effects, but controlled studies are still needed to confirm such results [135]. As stimulation of 5-HT_{2A} receptors can reduce dopamine release in the mesolimbic, nigrostriatal, and mesocortical pathways, it is presumed that binding of DMT at serotonergic receptors is able to decrease the release of dopamine, reducing activity in the reward or pleasure center of the brain. Result from a preliminary observational study of ayahuasca-assisted treatment for problematic substance use and stress conducted in Canada highlights ayahuasca as a potential treatment for cocaine dependence, with a statistically significant reduction in use (by self-report) that is greater than the reduction in either tobacco or alcohol use [176]. Ayahuasca is also reported to reduce also addiction in alcoholic patients, but results remain inconclusive. Studies reveal that ayahuasca prevented significantly the development of alcohol-induced behavioral sensitization in mice, reversing long-term drug effects expression and inhibiting the reinstatement of alcohol-induced behavioral [136]. The effect of the beverage on alcohol intake in rats was evaluated after 8 weeks of intermittent access to alcohol, during which animals received an administration of ayahuasca extract in the last 5 days [134]. Ethanol intake remained unchanged compared to the baseline level, but ayahusca reduced c-fos expression increased due to drug stimulus.

The use of ayahuasca is legal in Brazil in the context of religious use, since therapeutic use needs further evidences. Out of South America it is possible to use it legally also in the Netherlands, but syncretic churches exist in many European countries. Ayahuasca community is well-established internationally, enabling commercialization and availability almost worldwide [67].

14.2.5 *Coptis japonica* Makino (Ranunculaceae)

Coptis japonica is a medicinal plant native from Asia used as an anti-bacterial and anxiolytic agent due to the presence of benzylisoquinoline alkaloids in roots such as berberine and palmitine. Among them, berberine (Fig. 14.5a) is the main product, associated to a wide range of pharmacological properties including anti-inflammatory and anti-amnesic actions [59]. This compound caused a decrease in dopamine content in neuronal cells by inhibiting tyrosine hydroxylase activity, suggesting a possible modulation on morphine-induced adverse effects *in vivo*. Studies revealed that pre-treatment with a methanolic extract of *Coptis japonica* significantly reduced morphine-induced CPP in mice, through a mechanism that may involve the modulation of c-Fos proteins, p-CREB expression, dopaminergic and glutamatergic systems [96, 98]. Berberine administration blocked the depression and anxiety behavior of opioid abstinence in mice, blocking the increase in hypothalamic corticotropin-releasing factor expression, the tyrosine hydroxylase expression in locus coeruleus and decreasing the hippocampal brain-derived neurotrophic factor (BDNF) [100]. Berberine is also found to reduce the ethanol-induced CPP, modulating induced rewarding effects in mice. Coptisine (Fig. 14.5b) is other

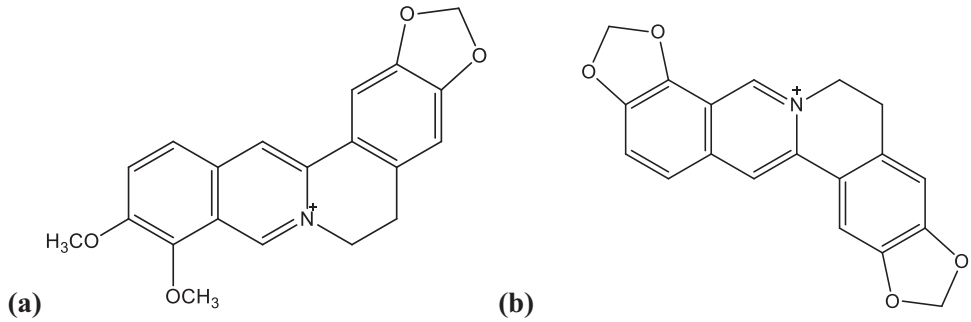


Fig. 14.5 Structures of the *Coptis* alkaloids: (**a**) berberine and (**b**) coptisine

alkaloid found in *Coptis japonica* and associated with the reduction of morphine withdrawal symptoms in mice, due to the *in vitro* MAO-A inhibitory activity described.

14.2.6 *Papaver rhoeas* L. (Papaveraceae)

Aerial parts of corn poppy are commonly used in preparations as a pain reliever and for cough and sleep disorders. Among the compounds described for the species, (−)-tetrahydropalmatine, and a number of benzylisoquinoline and papaverine-type alkaloids were found, contributing for the pharmacological activities described. The administration of a hydroalcoholic extract of *Papaver rhoeas* before morphine injection in opioid-dependent mice demonstrated a reduction on jumping and diarrhea, due to a mild opioid effect and antagonism in dopaminergic and cholinergic systems [146]. The chronic intraperitoneal administration of the same extract also reduced the acquisition and expression of morphine-induced behavioral sensitization in mice [162].

14.2.7 Isoquinoline Alkaloids

Tetrahydropalmatine (THP, Fig.14.6a) is a bioactive alkaloid present as a racemic mixture in herbal preparations with analgesic and sedative activities, consisting of the species *Corydalis ambigua* Cham. & Schltdl. (Papaveraceae) and *Stephania tetrandra* S. Moore (Menispermaceae) [172]. The levo isomer (−)-THP, known as rotundin, has an important role in the therapeutic effects of these preparations and its medicinal use as a non-opioid analgesic and anxiolytic agent is approved by the Chinese government [172, 186]. This isomer is a selective dopaminergic antagonist, with a strong affinity for D1 receptors and modulating both D2 and D3 receptors [114], suggesting that it can be useful for chemical dependence treatment. Additionally, interaction with α-adrenergic and GABAergic systems are reported for this alkaloid [61]. On the other side, the dextro isomer (+)-THP causes a selective dopamine depletion, associated with the toxicological profile described for the administered preparations [106]. Pre-clinical evidences support the use of (−)-THP in the treatment of cocaine addiction, due to an attenuation in cocaine reinforcing and rewarding effects in rat models. The administration of this alkaloid also reduced the hyperlocomotion and climbing behavior induced by methamphetamine in rodents, associated with the regulation of 5-HT neuronal activity and dopamine D3 receptor expression [194]. A number of clinical trials conducted in China with (−)-THP showed promising results due to its ability in reducing heroin craving and promoting detoxification in addicts [191]. The clinical examination for this compound as effective in human cocaine addict populations is still required. Of note, preparations containing this compound have illegal status in U.S. and therefore have poor quality and some toxic effects associated.

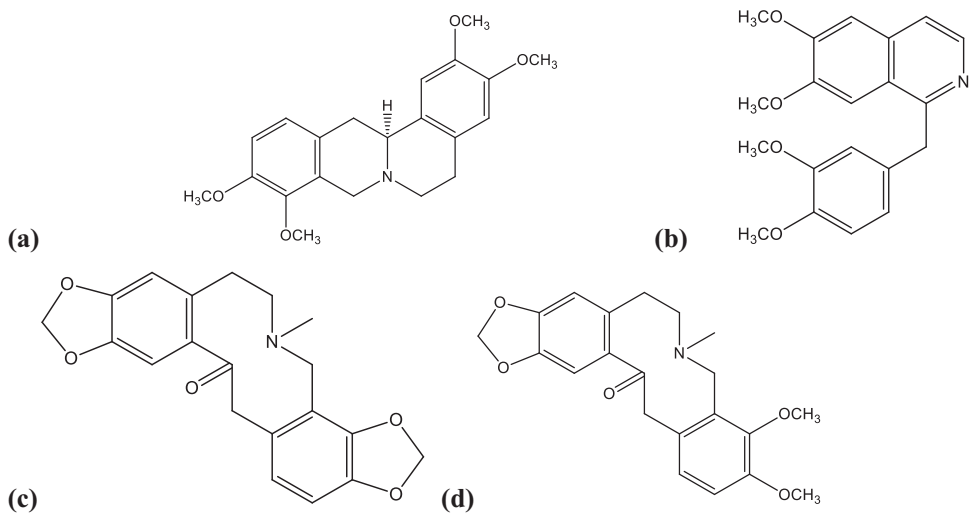


Fig. 14.6 Structures of the isoquinoline alkaloids tetrahydropalmatine, THP (**a**), papaverine (**b**), protopine (**c**) and allocryptopine (**d**)

The opium alkaloid papaverine (Fig. 14.6b), a smooth muscle relaxant, demonstrated positive effects due to prevention or reversal of naloxone-precipitated withdrawal contractures in an *in vitro* acute morphine-dependent guinea-pig ileum model [22]. Such an effect was attributed to a putative effect on μ and κ opioid receptors and interaction with cholinergic system.

Some alkaloids isolated from the South American medicinal species *Argemone mexicana* L. (Papaveraceae) and *Aristolochia constricta* (Aristolichiaceae) produced a significant influence in the guinea-pig ileum contraction induced by opiate withdrawal [24]. In this study, the isoquinoline alkaloids exerted their effects as agonists on both μ and k opioid receptors, while the protopine alkaloids reduced morphine withdrawal due to their anticholinergic properties. The major compounds found in *Argemone mexicana* are protopine (Fig. 14.6c) and allocryptopine (Fig. 14.6d), so this effect can be associated with these isoquinoline alkaloids [23].

14.2.8 *Camellia sinensis* L. Kuntze (Sapindaceae)

The aminoacid L-theanine (Fig. 14.7a) is found in green tea leaves and marketed as a dietary supplement in U.S. to reduce stress and improve cognition. Using a model for spontaneous opioid withdrawal in human opioid addicts, the administration of this compound attenuated opioid-withdrawal signs in morphine-dependent rhesus monkeys and produced anxiolytic-like effect in mice without affecting the motor behavior, with a quick onset and duration of action persisting for 2.5 hours. [189]. Moreover, a number of clinical studies conducted with L-theanine confirmed its positive effects on stress-related conditions, depression and anxiety [65, 66]. The mechanism of action purposed involves antagonistic effects on NMDA receptors and increase on levels of GABA, dopamine and serotonin [78, 90, 193]. On the other hand, caffeine (Fig. 14.7b), a methylxanthine component of green tea, increased withdrawal signs in morphine-dependent rats producing opioid-like symptoms [83], precipitated withdrawal signs in opioid-addicted monkeys and induced opioid withdrawal signs in some normal monkeys [3]. Theophylline (Fig.14.7c) is known to antagonize morphine antinociceptive effects and produced quasi-abstinence opioid signs, intensified by naloxone and suppressed by heroin [32], proving that adenosine antagonists influence opioid withdrawal, especially at A1 receptors [21]. L-theanine and methilxantines occur concomitantly in green tea

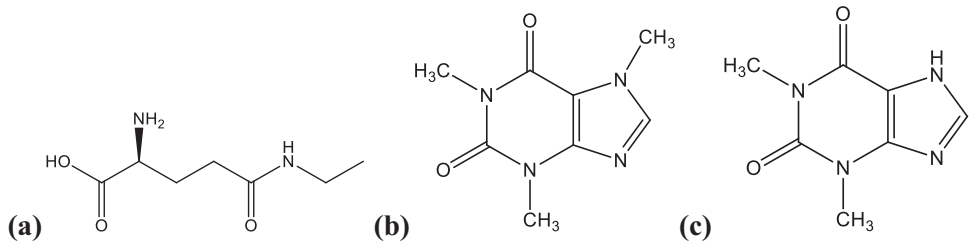


Fig. 14.7 Structures of the green tea compounds L-theanine (**a**), caffeine (**b**), theophylline (**c**)

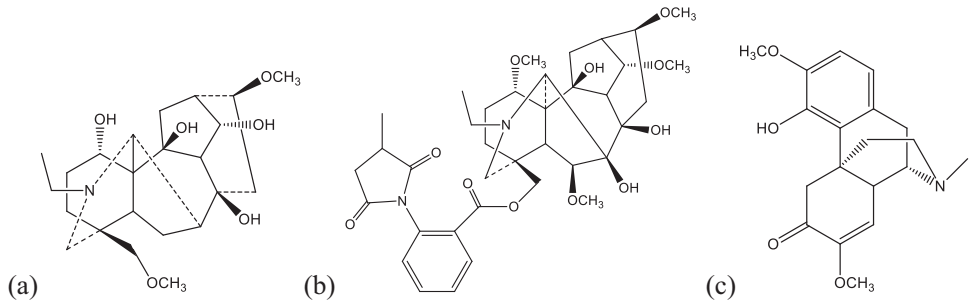


Fig. 14.8 Structures of jadwarine-A (**a**), methyllycaconitine (**b**) and sinomenine (**c**)

preparations, and L-theanine has been shown to inhibit caffeine's excitatory effects at the concentration regularly associated with drinking tea [77]. However, studies related to the effects of *Camellia sinensis* effects on opioid withdrawal signs in rodents and humans remain to be performed.

14.2.9 Other Species

Brugmansia arborea (L.) Lagerh. (Solanaceae) is a species used in folk South American medicine as an analgesic and antispasmodic, which contains a number of tropane alkaloids as atropine, scopolamine and nor-hyoscine. All of the compounds significantly reduced *in vitro* morphine withdrawal on guinea-pig ileum in a dose-dependent manner, possibly due to their anticholinergic activity [20]. Extract, fractions and isolated alkaloids were *in vivo* assayed in opioid-dependent mice, attenuating the development and expression of dependence with no effects on acquisition of morphine tolerance [121]. A methanol extract of *Brugmansia arborea* attenuated in part the morphine-induced motor activity and blocked the CPP induced by morphine in mice [16]. The same study reported that cocaine-induced hyperactivity was also abolished by the extract, with no effects on cocaine-induced CPP, demonstrating a complex mechanism of action for *B. arborea*, possibly by modulation of the dopaminergic and cholinergic systems.

The dried roots of *Delphinium denudatum* Wall. ex Hook. f. & Thomson (Ranunculaceae), known as Jadwar, have several medicinal uses in Asia as a pain reliever, anticonvulsant, sedative and anti-fatigue agent [36]. The concomitant oral administration of an aqueous *Delphinium denudatum* extract with morphine caused a dose-dependent attenuation on the naloxone-precipitated jumping in mice, therefore reducing withdrawal symptoms [197, 198]. Some norditerpenoids alkaloids were described for the species, such as jadwarine-A (Fig. 14.8a), showing a competitive inhibitory effect for acetyl and butyrylcholinesterase activities [5]. The putative mechanism of action seems to be independent to opioid receptors and associated with cholinergic and blocking activity at α7-type neuronal nico-

tinic receptor, as reported for the main alkaloid, methyllycaconitine (Fig. 14.8b) [149].

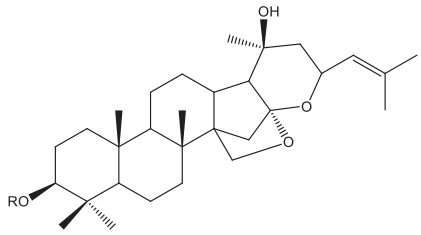
Sinomenium acutum (Thunb.) Rehder & E.H. Wilson (Menispermaceae) dried stems (Caulis sinomenii) are used for thousands of years in Tradicional Chinese Medicine for the treatment of rheumatic diseases. Extracts of Calis sinomenii and its main alkaloid, sinomenine (Fig. 14.8c), were evaluated on morphine-induced-CPP in mice [126]. The results showed a suppression on morphine place preference and the modulation of histamine brain levels in morphine-dependent mice.

14.3 Plants Containing Triterpenes and Steroids as Active Constituents

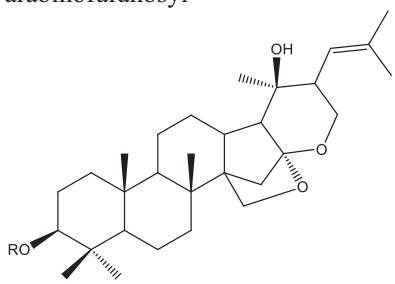
Terpenoids constitute a large and diverse group of secondary metabolites derived from isoprene units (C_5) linked in a head-to-tail manner. Usually, isoprene units are synthetized from mevalonic acid pathway, but an alternative biosynthetic pathway derived from 1-deoxy-D-xylulose-5-phosphate is also described. The extension of isoprene units generates structures multiples of C5, which can be later cyclized or chemically modified. The squalene (C30) is a precursor of triterpenoids and steroids, produced after a series of cyclization and additional reactions. Among the plant-derived compounds of pharmacological importance belonging to this class, saponins and cardioactive glycosides are the main metabolites with current clinical use. Some examples of medicinal plants containing triterpenes and steroids as active components are liquorice roots (*Glycyrrhiza glabra* L., Fabaceae), source of glycyrrhizin, a saponine with reported corticosteroid-like activity and sweet taste and used as demulcent, mild expectorant and for inflammatory conditions and *Digitalis* spp., source of digitoxin and digoxin administrated for congestive heart failure. For further reading, see Devick [40].

14.3.1 *Bacopa monnieri* (L.) Wettst (Plantaginaceae)

In the Indian subcontinent, *Bacopa monnieri* is a common medicinal species used in Ayurvedic medicine as a brain tonic, for memory loss, insomnia and a number of neuropsychiatric disorders. Sterol glycosides were described for the plant, but the pharmacological effects are associated to the presence of dammarane triterpenoid glycosides, mainly bacoside A, the bioactive compound. Further studies characterized this compound as a mixture of four saponins (bacoside A3, bacopaside II, bacopaside X and bacopasaponin C, Fig. 14.9). The administration in mice of a polar extract of *Bacopa monnieri* containing bacoside A3 significantly reduced both expression and development of tolerance to morphine analgesia [151]. The extract blocked the effect of calcium channels, resulting in the modulation of adenyl-cyclase activation by opioid receptors. The same extract demonstrated a decrease in the morphine withdrawal-induced hyperactivity in mice. Samples of mice striatal tissue were also analyzed for dopamine, serotonin and their metabolites, and the result was significant lowered levels of 3,4-Dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), dopamine and 5-Hydroxyindoleacetic acid (5-H1AA) induced by morphine, therefore demonstrating an antidopaminergic/serotonergic activity [152]. Chronic administration of a standardized *Bacopa monnieri* extract (4 μg bacoside A3/mg extract) significantly inhibited opioid withdrawal induced depression in mice [153]. A potent antioxidant activity was also demonstrated for the extract, exerting a protective effect against morphine-induced cerebellar toxicity and attenuating histopathological changes [165]. The beneficial effects of *Bacopa monnieri* extracts on morphine-withdrawal symptoms seem to be associated with the antioxidant, anticholinergic and calcium-channel antagonist activities of the saponins.



Bacoside A3 R= α-L-arabinofuranosyl(1→2)-[β-D-glucopyranosyl-(1→3)]- β-D-glucopyranosyl
Bacopaside X R= α-L-arabinofuranosyl(1→2)-[β-D-glucopyranosyl-(1→3)]- α-L-arabinofuranosyl



Bacopaside II R= α-L-arabinofuranosyl(1→2)-[β-D-glucopyranosyl-(1→3)]- β-D-glucopyranosyl

Bacopasaponin C = R=α-L-arabinofuranosyl(1→2)-[β-D-glucopyranosyl-(1→3)]- α-L-arabinofuranosyl

Fig. 14.9 Structure of bacoside A

14.3.2 *Panax ginseng* C.A. Meyer (Araliaceae)

The roots of wild ginseng have been used in Chinese Traditional Medicine preparations over centuries as a stimulant or an "elixir of life". The bioactive products found in ginseng are the triterpene saponins known as ginsenosides, containing tetracyclic and pentacyclic cores. Standardized ginseng extracts are used in a number of phytomedicines used with alleged therapeutic effects as adaptogens, reducing the stress-related symptoms. Studies suggest that ginseng saponins prevent behavioral hyperactivity induced by psychomotor stimulants, including nicotine, morphine and cocaine. The chronic administration of ginseng extract was able to inhibit the analgesic and hyperthermic effects of morphine [15]. A standard ginseng extract also mitigated the morphine-induced dopamine receptor supersensitivity, the development of morphine-induced tolerance and physical dependence in mice [87]. Moreover, the morphine-induced antinociception was prevented by pretreatment with ginseng total saponins due to their non-opioid interactions. In fact, catecholaminergic and serotonergic mechanisms are involved in the antagonism of morphine-induced antinociception by ginseng in mice. Administration of wild ginseng extract proved to be effective at inhibiting the anxiety and depression behaviors associated to morphine withdrawal, in response to a modulation of corticotrophin-releasing factor and neuropeptide Y systems on hypothalamus [99]. The mechanism of action for ginseng saponins on morphine withdrawal symptoms seems to be associated to multiple pharmacological interactions between dopamine receptors and a serotonergic/adenosine A_{2A}/δ-opioid receptor complex [88]. The ginseng metabolites also seem to modulate the GABA

receptor complex, ameliorating the morphine dependence. Studies revealed that the ginsenosides inhibit the morphine-6-dehydrogenase, responsible for the conversion of morphine into its toxic metabolite, morphinone, playing an important role in the development of both morphine-induced analgesic tolerance and dependence. The effect is therefore associated with morphine detoxification process, increasing the hepatic glutathione levels. Wild ginseng also showed significant inhibition on morphine-induced hyperactivity, increasing the c-Fos expression in nucleus accumbens and the expression of tyrosine hydroxylase enzyme in ventral tegmental area. Studies with both crude extracts and isolated ginsenosides showed significant results on morphine withdrawal symptoms [192]. The chronic administration of ginsenoside Rg1 (Fig. 14.10) significantly improved the spatial learning capacity impaired by chronic morphine administration and reversed the long-term potentiation impaired by morphine, restoring neural plasticity due a mechanism dependent to NMDA receptors [147].

Studies described that the administration of ginseng total saponins during nicotine treatment in mice prevented not only nicotine-induced hyperactivity and CPP but also postsynaptic dopamine receptor supersensitivity [86]. Further investigations analyzed the effect of ginseng saponins on dopamine release in the striatum of freely moving rats induced by nicotine administration, using the microdialysis technique [168]. Results showed that the extract inhibited the striatal DA release stimulated by local infusion of nicotine, possibly due to a modulation on presynaptic nicotinic acetylcholine receptors or receptor-operated Na^+ channels in dopaminergic nerve terminals. The total saponins also decreased the nicotine-induced Fos protein expression in the nucleus accumbens and striatum of mice, reflecting the attenuation of nicotine-induced effects by *Panax ginseng* related with the inhibition of the dopaminergic transmission [89].

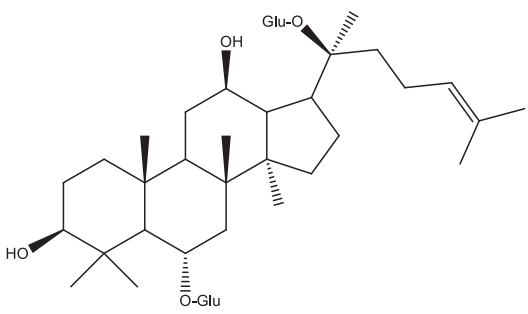


Fig. 14.10 Structure of ginsenoside Rg1

The bioactive fraction of saponins also inhibited the cocaine-induced reverse tolerance and CPP, promoting the development of postsynaptic dopamine receptor supersensitivity in mice). The extract administration caused a suppression in the development of reverse tolerance and the reappearance of sensitization to methamphetamine and cocaine in mice [180]. The neurochemical basis for the prevention of withdrawal symptoms in mice is related to the attenuation of the cocaine-induced release of dopamine, preventing the rebound increase during acute withdrawal [130].

14.3.3 *Withania somnifera* (L.) Dunal (Solanaceae)

The whole plant has medicinal uses, but freshly roots of Indian ginseng have therapeutic purposes in Ayurvedic medicine for the treatment of anxiety, neurosis and sexual debility [37]. Chemically, the species is characterized by the presence of alkaloids, steroids and unusual steroidal lactones, known as withanolides, considered the main bioactive compounds. Chronic treatment with *Withania somnifera* root extract in mice attenuated the development of tolerance to the analgesic effect of morphine and the naloxone- induced jumping, proving to be useful to mitigate symptoms of morphine withdrawal [93]. The administration of the extract also prevented the spine density reduction in the nucleus accumbens shell in spontaneous and pharmacologically precipitated morphine withdrawal [80]. Another study showed that *Withania somnifera* extract injection (100 mg/kg) prevented the acquisition and expression of morphine elicited CPP. The authors also characterized the effect using receptor-binding assays, pointing out to an affinity for

GABA-B receptors and to a less extent for μ-opioid receptors [159]. The *in vitro* incubation of the plant extract alone or concomitantly with morphine in neuroblastoma SH-SY5Y cells prevented opioid receptors down-regulation elicited by morphine, relating to the *in vivo* modulation of morphine-mediated analgesia by the plant extract [26]. Recently, a PPARγ-mediated mechanism in the effects of *Withania somnifera* extract on morphine-mediated nociception was also demonstrated [27].

Studies also showed that roots extract impaired the ethanol self-administration in rats by blocking GABA-B receptors, altering the alcohol-elicited CPP and conditioned place-aversion (CPA) [141]. Additionally, it was demonstrated that the same extract significantly reduced the spontaneous neuronal firing of rat dopaminergic neurons stimulated by morphine and alcohol in the ventral tegmental area, via GABA-A mechanism. The morphine- and alcohol-elicited increases of dopamine in the shell of the nucleus accumbens was also significantly prevented by the extract, as measured by *in vivo* brain microdialysis [12].

14.3.4 *Crocus sativus* L. (Iridaceae)

Saffron is a golden-colored spice of strong flavor, commonly used in the Mediterranean cuisine and extracted from the dried stigma present in *Crocus sativus* flowers. The saffron characteristic color is due to the presence of crocin (Fig. 14.11a), a water-soluble carotenoid with a number of pharmacological activities, such as antidepressant, anti-inflammatory, neuroprotective and anticarcinogenic [128]. Safranal (Fig. 14.11b) is a terpene aldehyde and the major constituent present in the essential oil, responsible for the distinct aroma of this spice, whilst its β-D-glycoside picrocrocin (Fig. 14.11c) is associated with the strong flavor described.

The antinociceptive activity reported for an aqueous extract of saffron was partially blocked by naloxone, demonstrating an interaction with the opioid system [72]. Saffron also inhibited the acquisition and expression of morphine-induced behavioral sensitization in mice, reducing the morphine-induced hyperactivity. Aqueous and ethanolic extracts of saffron stigma and isolated crocin were investigated in the morphine-withdrawal model in mice after intraperitoneal injection concomitantly with morphine [69]. Results showed that both extracts and crocin attenuated the severity of jumping in mice precipitated by morphine withdrawal, but safranal exaggerated withdrawal symptoms, possibly due to a partial opioid agonist effect. Crocin also decreased the acquisition of the morphine-induced CPP and the reinstatement of morphine-induced CPP, when administered before a single dose of morphine in animals after extinction of morphine-induced CPP. In rat model of neuropathic pain, preemptive administration of crocin during chronic constriction injury maintained morphine analgesia throughout time, preventing the development of morphine tolerance and suppressing BDNF levels increase induced by neuropathic pain [160]. Clinical trials conducted with

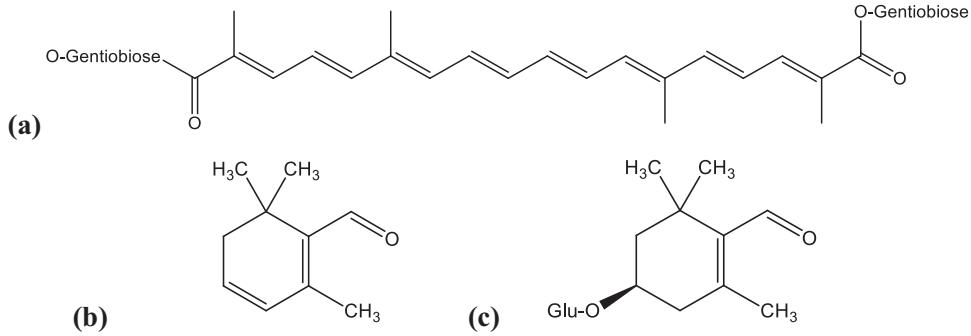


Fig. 14.11 Structure of saffron bioactive compounds: (**a**) crocin, (**b**) safranal and (**c**) picrocrocin

patients under methadone maintenance treatment receiving crocin showed beneficial effects on their mental health and improved their metabolic profiles [50, 82]. Findings indicate that crocin can be recommended as an adjunct to methadone in opioid withdrawal protocols because of the ability to improve the quality of life, reducing opioids side effects in these patients.

14.3.5 *Salvia* spp. (Lamiaceae)

Some species of *Salvia* are used worldwide in folk medicine due to their multiple pharmacological actions on CNS, as anti-inflammatory, analgesic, anticonvulsant and sedative agents. Among the compounds found in these species, diterpenes known as tanshinones are allegedly the bioactive metabolites, highlighting miltirone, carnosic acid and carnosol [75]. The neoclerodane diterpene salvinorin A is the major active compound in the hallucinogenic species *Salvia divinorum*, and one of the most potent naturally occurring hallucinogen thus far isolated. This compound is considered as an emerging target for next-generation non-nitrogenous analgesic drugs due to its potent and selective kappa-opioid receptor binding affinity [158]. Moreover, several *Salvia* species demonstrated antiaddictive properties.

The administration of the ethanol extract of *Salvia leriifolia* leaves reduced in a dose-dependent manner the jumping behavior in morphine withdrawal symptoms induced by naloxone in mice. At a 500 mg/kg dose, the extract was as effective as diazepam at 5 mg/kg, but the effect was antagonized by aminophylline, indicating a possible effect of the extract on the adenosine system [70]. A *Salvia limbata* methanol extract obtained from macerated aerial parts demonstrated a reduction of withdrawal signs of morphine when administered before naloxone challenge in mice. The extract also displayed a central antinociceptive on hot-plate test, reversed by the administration of naloxone [7]. The putative mechanism of action for *Salvia limbata* involves interaction with opioid and adenosine receptors, since a number of neoclerodanes are reported as opioid receptor ligands [158]. Other studies showed that *Salvia hypoleuca* aerial parts extract produced a significant inhibition of pain and the development of the incidence of escape jumps observed in morphine dependence mice [79] and *Salvia officinalis* leaves extract promoted antinociceptive effects and the decrease of both tolerance and dependence induced by repeated morphine administration in rats [63].

Several experiments demonstrated the efficacy of the extract of dried roots of *Salvia miltiorrhiza*, a species native to Japan and China, in reducing voluntary alcohol intake in alcohol-preferring rats. Further experiments showed that a standardized extract of the species delayed dose-dependently the acquisition of alcohol drinking behavior in alcohol-preferring rats that had never experienced alcohol before the study, supporting other pre-clinical studies [18, 181]. A *S. miltiorrhiza* extract, containing 21% total tanshinones and 4.3% miltirone, reduced the reinforcing and motivational properties of alcohol in rats [110]. The same effect was observed when alcohol-naive and alcohol-experienced rats were treated with miltirone and exposed to the 2-bottle choice regimen, confirming the compound as the responsible for the anti-addictive activity [33]. The mechanism of action is connected to the presence of diterpenes in the roots of Salvia *miltiorrhiza* such as miltirone (Fig. 14.12a), a low-

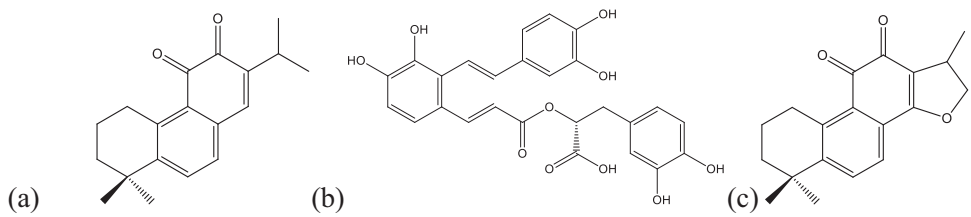


Fig. 14.12 Structure of bioactive compounds from *Salvia* spp.: (**a**) miltirone, (**b**) salvianolic acid A and (**c**) cryptotanshinone

affinity ligand for benzodiazepine site in $GABA_A$ receptors that is able to mitigate the withdrawal symptoms associated with the long-term administration of alcohol [127]. Also, salvianolic acid A (Fig. 14.12b) is able to protect the liver of rats against chronic alcohol-induced injury, reducing the presence of lipid droplets and the plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglyceride (TG), alcohol and ammonia levels in blood by a SIRT1/β-catenin pathway [167]. The compound cryptotanshinone (Fig. 14.12c) activated the phosphorylation of AMP-activated protein kinase (*AMPK*), sirtuin 1 (*SIRT1*), and nuclear factor E2-related factor 2 (*Nrf2*) proteins countering ethanol-promoted hepatic steatosis in mice [129].

14.3.6 *Polygala telephioides* Willd. (Polygalaceae)

This is a species widely distributed in southern China and it has been used as a detoxification agent for heroin poisoning. In mice, the methanolic extract of the plant was capable of antagonizing the analgesic effect induced by morphine and reduced the plasmatic levels of the drug. When coadministered with chronic use of morphine, the extract significantly decreased the nalaxone-induced jumping behavior [46]. The extract of the plant roots also attenuated cocaine induced hyperlocomotion and conditioned place preference, possibly via the activation of the adenosine A_{2A} receptors [169]

14.4 Plants Containing Essential Oils as Active Constituents

Essential oils are widely used in the flavor, food, fragrance, and cosmetic industries in many applications. They are complex mixtures containing mostly monoterpenoids and sesquiterpenoids. (−)-α-Thujone, obtained from the oil of wormwood (*Artemisia absinthum*), is one of the most notorious monoterpenes. It is the major bioactive ingredient of the hallucinogenic liquor absinthe, a favorite of artists and writers in the nineteenth and early twentieth centuries. It is widely held to have been responsible for psychoses and suicides, possibly including that of Vincent van Gogh. Matricin and chamazulene, the major components of the extract of German chamomile (*Matricaria chamomilla*) inflorescences, which have anti-inflammatory properties, are examples of known sesquiterpenoids.

Cumin, *Cuminum cyminum* Linn., Apiaceae, is native from Mediterranean region but, due to its largely used in culinary, it is widely cultivated in Asian countries. Its essential oil has depressant CNS effects, bounding to $GABA_A$ receptors [163]. Animal studies have shown that the *C. cyminum* essential oil was able to decrease behaviors related to morphine withdrawal and the tolerance to morphine-induced analgesia [60]. Another plant with similar characteristics is *Pimpinella anisum* L. Apiaceae, whose essential oil reduced the morphine-induced conditioned place preference (CPP) in mice, probably through a GABAergic mechanism [161]. *Zhumeria majdae* Rech. f. & Wendelbo Lamiaceae presents an essential oil cointaing monoterpenes such as linalool, camphor and borneol, which inhibited the jumping behavior during morphine withdrawal syndrome in mice [73].

Kelussia odoratissima Mozaff., Apiaceae is a flavor species used in Iranian traditional medicine to treat hypertension and inflammation. The main constituent of the essential oil of this plant is the phthalide z-ligustilide (Fig. 14.13), which has voltage-dependent calcium channel blocking properties. Chronic treatment with the essential oil relieved symptoms of morphine withdrawal in mice [148]. Another endemic aromatic medicinal plant of Iran is *Thymus daenensis* Celak, Lamiaceae, whose extract and essential oil atten-

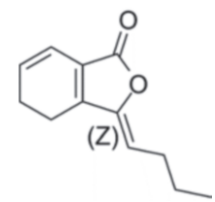


Fig. 14.13 Chemical structure of z-ligustilide

uated morphine withdrawal behaviors in mice [85]. Similarly, the oil of *Zingiber officinale* Roscoe Zingiberaceae, a well-known condiment and used worldwide that completely prevented the tolerance for morphine in mice. The effect is related to the Ca^{+2} L type channel blocker [38].

Nigella sativa L., Ranunculaceae has been traditionally used for the treatment of several disorders. Medicinal properties of *N. sativa* have been attributed to its seeds extracts and/or oil. The oil attenuated tolerance and dependence induced by morphine and tramadol in mice [1, 2] and the seed extract reduced the morphine-induced conditioned place preference in rats [10]. The major constituent of *N. sativa* is the quinonic compound thymoquinone, which also attenuated the morphine tolerance and dependence in mice [74].

14.5 Plants Containing Flavonoids as Active Constituents

Flavonoids are polyphenolic compounds comprising 15 carbons, with two aromatic rings connected by a three-carbon bridge. In plants, flavonoids are involved in such diverse processes as UV protection, pigmentation, stimulation of nitrogen-fixing nodules and disease resistance. The main subclasses of flavonoids are flavones, flavonols, flavan-3-ols, isoflavones, flavanones and anthocyanidins. Examples of flavonoids with pharmacological activity are the isoflavones (genistein and daidzein) and the coumestan (coumestrol) from lucerne and clovers (*Trifolium* spp), which have sufficient oestrogenic activity to seriously affect the reproduction of grazing animals such as cows and sheep and are termed phyto-oestrogens.

14.5.1 *Morinda citrifolia* L (Rubiaceae)

Morinda citrifolia, commonly known as "noni," is a small tropical tree that grows widely in Southeast Asia. The different parts of this plant (e.g., fruit, leaf, bark, root, flower, and seed) have long been employed in folklore medicine to treat a broad range of diseases including diabetes, hypertension, arthritis, depression, senility, menstrual difficulties, headaches, and drug addiction. The methanolic extract of *M. citrifolia* unripe fruits, containing the coumarin scopoletin (Fig. 14.14a) and the flavonoid rutin (Fig. 14.14b), effectively reversed the ethanol [84], heroin [131] and methamphetamine-induced conditioned place preference [139] in mice and rats. The mechanism is not completely understood but it is related to the antagonism activity in dopaminergic D_2 receptor and MAO inhibition.

14.5.2 *Pueraria lobata* (Willd.) Sanjappa & Pradeep (Fabaceae)

Kudzu (*Pueraria lobata*) is a vine indigenous to eastern Asia. It has been used as an herbal remedy in China to treat a variety of disorders, including neck pain, eye pain, fever, and measles. More recently, kudzu flower root is reported to be used in China for the treatment of alcohol addiction. Puerarin (Fig. 14.15a), daidzin (Fig. 14.15b), and daidzein (Fig. 14.15c) are three of the major

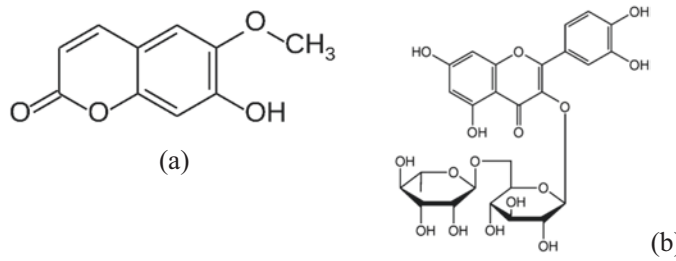


Fig. 14.14 Chemical structure of (**a**) scopoletin and (**b**) rutin

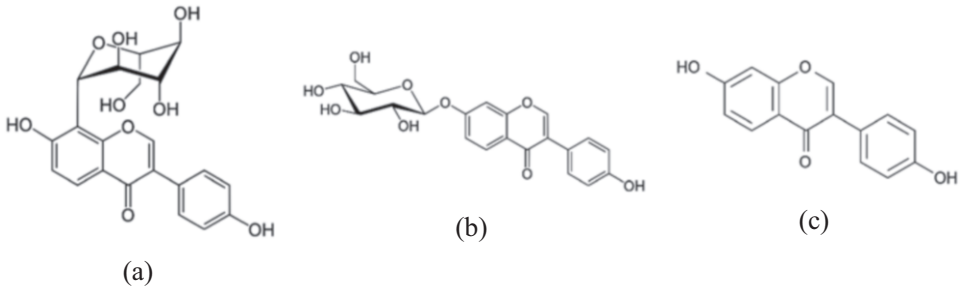


Fig. 14.15 Chemical structure of (**a**) puerarin, (**b**) daidzin, and (**c**) daidzein

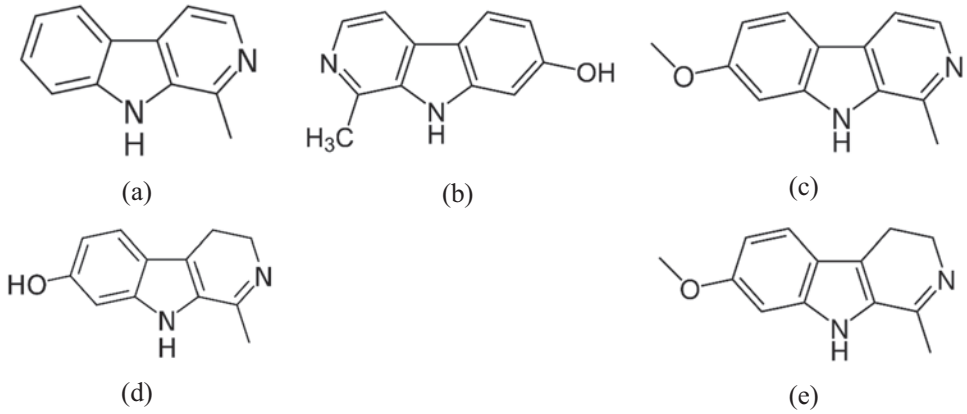


Fig. 14.16 Chemical structures of the indole beta-carboline type alkaloids (**a**) harmane, (**b**) harmol, (**c**) harmine, (**d**) harmalol, and (**e**) harmaline present in *Passiflora incarnata*

isoflavonoid compounds identified in the extract of *P. lobata*. These flavonoids are effective in the reduction of alcohol consumption in rats [109]. In humans, a standardized kudzu extract (NPI-031) reduced alcohol drinking in non treatment-seeking male heavy drinkers with no adverse events, changes in vital signs, blood chemistry, renal or liver function [109]; and in binge drinking paradigm [142]. Both puararin and daidzin seem to have inhibitory action in benzodiazepinic receptors [137]. Moreover, daidzin inhibits ALDH-2, making the decreased drinking be attributed to aversive properties of acetaldehyde accumulated during alcohol consumption in a disulfiram-like mechanism [81, 95, 107, 155].

Studies have compared the effects of daidzin, daidzein and pueranin on the suppression of ethanol intake. Daidzine is more effective than the others in all comparative studies performed, while pueranine had a lower, but still significant suppressor effect. Daidzeine was ineffective [103, 155].

14.5.3 *Passiflora incarnata* L. (Passifloraceae)

Passiflora incarnata is used in phytomedicine, with alleged therapeutic properties such as anxiety, nervousness, and insomnia treatments. Interestingly, in India, it is the species traditionally used to treat morphine's dependence. The chemistry of *P. incarnata* is complex, and the active constituents include flavonoids and alkaloids as the bioactive compounds. The indole beta-carboline alkaloids, namely harmane, harmol, harmine, harmalol, and harmaline (Fig. 14.16), are minoritary constituents of the

plant and act as monoamine oxidase inhibitors. The flavonoids represent 2.5% of the plant compounds, which include vitexin, isovitexin, orientin, isoorientin, kaempferol, apigenin, and chrysin.

Preclinical studies evidence beneficial properties of *P. incarnata* as a treatment for addictive behaviors linked to substances such as nicotine [14, 17, 41], and benzodiazepines [44]. A standardized extract of *P. incarnata*, containing only flavonoids (Fig. 14.17), reversed the analgesia resulted from alcohol withdrawal syndrome in rats [164]. In mice, the benzoflavone moiety of *P. incarnata* decreased the anxiety induced by chronic ethanol abuse, as well as exhibited lower dependence level and fewer withdrawal signs compared with the ethanol treated mice [42]. Additionally, the benzoflavone moiety also prevented the development of tolerance and dependence of cannabinoids in mice [43].

In humans, a double-blind randomized controlled trial including 65 opiates addicts pointed that *P. incarnata*, alone or in combination with clonidine, was effective in the treatment of physical withdrawal symptoms of opioids. The combination *Passiflora*-clonidine, used during the withdrawal, might have a faster onset of action, whereas *Passiflora* extract can have therapeutic benefits in the management of opioids psychological withdrawal symptoms, suggesting that the plant extract might be an effective adjuvant agent in the management of opiate withdrawal [6].

14.5.4 Other Species

Matricaria chamomilla L. Asteraceae is an ancient European herb with several uses including anti-inflammatory, spasmolytic, and sedative. The plant contains flavonoids with benzodiazepine-like activity and inhibitory action on phosphodiesterase, leading to the increase cAMP levels. The repeated coadministration of the extract of *M. chamomilla* containing 0.3% apigenin, with morphine significantly attenuated the severity of the withdrawal syndrome probably due to the same mechanism reported for other phosphodiesterases' inhibitors

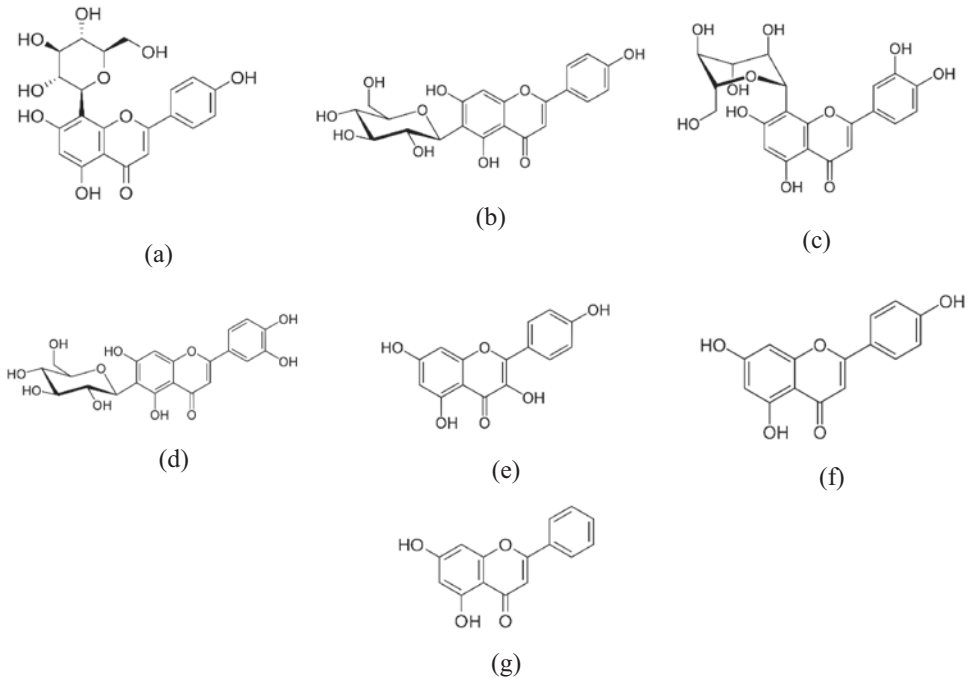


Fig. 14.17 Chemical structures of the flavonoids (**a**) vitexin, (**b**) isovitexin, (**c**) orientin, (**d**) isoorientin, (**e**) kaempferol, (**f**) apigenin, and (**g**) chrysin present in *Passiflora incarnata*

(e.g. 3-isobutyl-methylxanthine, nefiracetam or rolipram) [56].

The aqueous and ethanolic extract of aerial parts of *Rosmarinus officinalis* L., Labiatae reduced the signs of morphine withdrawal in rodents. Phytochemical characterization of the extracts indicated the presence of flavonoids, tannins, saponins and. Alkaloids, the latter detected only in the aqueous extract. Such constituents have opioid-like analgesic effect, which is reinforced by the fact that the antinociceptive activity of these extracts were inhibited by naloxone. Therefore, the morphine withdrawal relief could be attributed to an opioid-like action [71]. Similarly, total and polyphenolic extracts of fruits from *Carum copticum* (L.) C. B. Clarke C., Apiaceae, a plant endemic to India, Iran and Egypt, reduced morphine withdrawal syndrome [51].

Herbal preparations of *Scutellaria baicalensis* Georgi Lamiaceae are used in oriental traditional medicine for the treatment of many neuropsychiatric diseases for centuries. The aqueous extract of the roots of *S. baicalensis* and one of its main flavonoids, baicalin, have shown efficacy in reducing the morphine-induced conditioned place preference, probably due to the modulation of dopaminergic receptors [195].

Korean pear (*Pyrus pyrifolia* (Burm.) Nak.Rosaceae) has been used as a traditional medicine for alcohol hangover in Korea. The plant contains phenols, mainly flavonoids, including catechin, rutin, quercetin and kaempferol. In mice, the pear extract decreased the alcohol level in blood and increased the acetaldehyde levels by stimulation of the two-key alcohol-metabolizing enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) [101].

The leaves of *Jodina rhombifolia* (Hook. & Arn.) Reissek (Santalaceae) are commonly utilized as anti-alcoholic in Argentine folk medicine. Among the major chemical constituents found are phenolic compounds, tannins, C-glycosyl flavonoids, steroids, gums and mucilage. The lyophilized aqueous extract decreased ethanol intake and preference in adolescent male Wistar rats [173, 174].

14.6 Plants Containing Polysaccharides as Active Constituents

Polysaccharides refers to a class of structurally complicated and bulky carbohydrate synthesized from the condensation and dehydration of multiple single sugar molecules, considered as one of the four fundamental substances that constitute life. Currently, polysaccharides have been extracted from hundreds of species of plants and important and special biological activities have been associated to them.

Millettia pulchra Kurz var. *typica* Dunn, Fabaceae, also known as Yulangsan, is a traditional Chinese medicinal herb. The Yulangsan polysaccharide (YLSP) is the major active component of the roots and attenuated naloxone-induced morphine withdrawal signs in morphine dependent rats. Additionally, the polysaccharide presented modulatory effects in the expression of nitric oxide (NO) and NO synthase and also modulated the levels of monoaminergic neurotransmitters in the ventral tegmental area (VTA), hippocampus and *nucleus accumbens* [30]. YLSP also inhibited the reinstatement of morphine-induced conditioned place preference [31].

14.7 Plants Containing Multiple Compounds

14.7.1 *Nepeta menthoides* Boiss. & Buhse (Lamiaceae)

N. menthoides is an endemic specie of Iran, commonly known as "Ustukhuddoos" in folk medicine and prescribed for a number of nervous disorders such as epilepsy, anxiety, and depression, chronic pain and restlessness, gastrodynia, high blood pressure, bone pain, and rheumatism. Chemical analysis of the essential oil showed that the main terpenes are 1,8-cineol, α-terpineol, α-linalool, β-pinene, and α-pinene. Additionally, plant extract contains flavonoids (rosmarinic acid, salvianolic acids A and B, and caffeic acid), tannins, saponins and cardiac glycosides. A hydroalcoholic plant extract prevented the development of morphine

dependence and tolerance, and potentiated morphine antinociception in mice [150].

14.7.2 *Rhodiola rosea* L., Crassulaceae

Rhodiola rosea, known as golden root or rosenroot, grows in arctic regions of Europe and Asia, and due to the anxiolytic, antidepressive, and anti-stress properties associated, its derived phytomedicines are indicated as adaptogens. The rhizomes of the plant contain flavonoids, monoterpenes, triterpenes, phenolic acids, phenylethanol derivatives (salidroside and tyrosol), and phenylpropanoid glycosides such as rosin and rosavin (Fig. 14.18a). Among these, salidroside (Fig. 14.18b) is one of the most active constituents. In mice, *R. rosea* extract (containing 3% total rosavins, expressed as rosavin and 1% salidroside) abolished affective and somatic signs induced by nicotine withdrawal [119] and reduced the rewarding properties of nicotine [179]. The same extract also attenuated morphine tolerance and dependence [120] and cocaine-induced conditioned place preference [178]. Investigating the mechanism of action of *R. rosea* extract, it was found out an increase in 5-HT_{1A} receptors in the thalamic nucleus, which might promote the benefits observed in animals treated with this extract [113].

14.7.3 *Hypericum perforatum* L. Hypericaceae (St. John's Wort)

H. perforatum standardized extracts are extensively investigated and widely consumed due to their therapeutic effects on mood disorders, and action in mild to moderate depression. Several groups of bioactive natural products were identified in this plant species, among them naphtodianthrones (i.e., hypericin (Fig. 14.19a) and

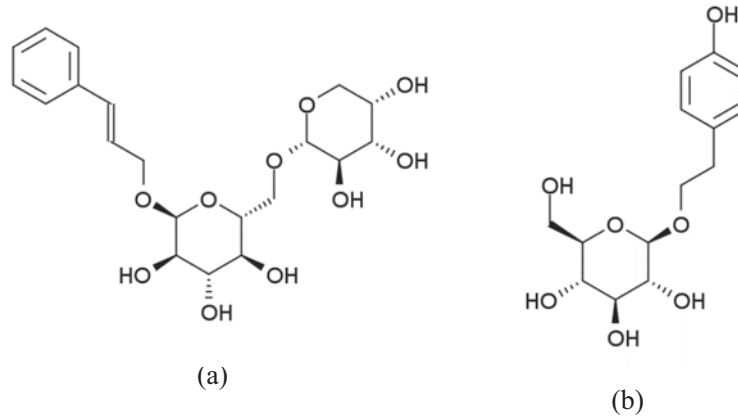


Fig. 14.18 Chemical structure of (**a**) rosavin and (**b**) salidroside

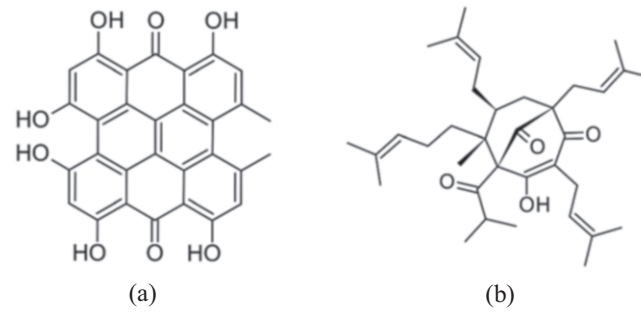


Fig. 14.19 Chemical structure of (**a**) hypericin and (**b**) hyperforin

pseudohypericin), phloroglucinols (i.e., hyperforin (Fig. 14.19b) and adhyperforin), flavonol glycosides (including quercetin, hyperoside or hyperin, rutin, isoquercitrin and isoquercitrin), biflavonoids (i.e., amentoflavone and biapigenin), phenylpropanes (including chlorogenic acid and caffeic acid), proanthocyanidins, tannins, xanthones, and certain amino acids (i.e., GABA). These constituents are present in different amounts in *Hypericum* extracts and therapeutic effects of extracts are associated to a possible synergism among the different constituents. In an alcohol-preferring genetic rats, intraperitoneal acute administration of an ethanolic extract of *H. perforatum* dose-dependently reduced alcohol intake in a two-bottle choice procedure [39]. Similarly, a *H. perforatum* CO_2 extract reduced ethanol self-administration in rats [145], and the reduction was more pronounced when the extract was associated with naloxone and naltrexone, providing evidence that extract and opiate receptor antagonists could act synergistically [144]. Additionally, a *H. perforatum* extract containing 50% flavonoids, 0.3% hypericin, and 4.5% hyperforin reduced nicotine withdrawal signs in mice after oral administration, The effect was linked to a serotonergic mechanism, in which the extract increased cortical 5-HT content in nicotine treated mice, with a concomitant increase of 5-HT_{1A} receptor [112]. Aqueous *H. perforatum* extract also attenuated abdominal constrictions both acutely and chronically when orally administered to heroin dependent rats [171]. In spite of all of this pre-clinical evidence, in a randomized, blinded, placebo-controlled clinical trial with 40 subjects, a hydroalcoholic *H. perforatum* extract (standardized in 0.3% hypericin) did not increase smoking abstinence [170].

14.8 Final Considerations and Future Directions

Drug abuse is one of the leading problems in human health nowadays, leading to tolerance and dependence as a main problem associated. Alcohol, opioids, nicotine, cocaine and amphetamines abuse are a main concern and the treatment of the psychosomatic syndrome induced by the withdrawal among users remains complicated. Due to the lack of pharmacological therapeutics to the treatment of drug addiction, plants and their active ingredients are promising choices to ameliorate drug-induced pharmacological changes such as tolerance, dependence, and withdrawal syndrome. Some plant families showed great potential in drug addiction therapy because of their bioactive compounds, mainly indole, isoquinoline and tropane alkaloids (Menispermaceae, Papaveraceae, Ranunculaceae, Rubiaceae and Solanaceae families), terpenes (Araliaceae, Lamiaceae, Plantaginaceae and Solanaceae families), essential oils (Apiaceae and Lamiaceae families), flavonoids (Rubiaceae and Asteraceae), and polysaccharides. Some families are distinguished for producing compounds belonging to different classes, such as Lamiaceae (essential oils and diterpenes) and Solanaceae (alkaloids and terpenes), while some species contain distinct bioactive compounds, such as *Passiflora incarnata* (alkaloids and flavonoids), *Hypericum perforatum* (polyphenols, phloroglucinol and naphthodianthrone derivatives) and *Rhodiola rosea* (flavonoids and phenylpropanoid derivatives).

Considering the mechanisms of action, the mentioned species offer a great variety of actions including symptomatic improvement (i.e. spasmolytic and sedative), opioid partial agonism (similar to replacement medications), neurotransmitter (cholinergic, adrenergic, dopaminergic, glutamatergic, and GABAergic) modulation, and interference with signaling pathways such as the cAMP and NO pathways. Although most of the literature in this issue is confined to animal studies, the results seem to be promising. Clinical studies, however, are needed to confirm the safety and efficacy of many of these herbal extracts and preparations. They could be used experimentally in detoxification centers along with standard pharmacological and psychological therapy. Traditional compound herbal formulae have been effective in a holistic approach, however, certain classes of compounds such as alkaloids and flavonoids have been demonstrated to be effective.

Therefore, screening for other potentially effective plants and natural products in these classes should be continued, and further research should be carried out to identify specific fractions and active components of the plants already tested.

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