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Review article

Plant derivatives in the treatment of alcohol dependency

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Abstract

The present review summarizes the findings of the effects of extracts of purified compounds from several plants on alcohol intake in alcohol-preferring rats. These include St. John's wort (*Hypericum perforatum*, HPE), kudzu (*Pueraria lobata*) and ibogaine (*Tabernanthe iboga*). Alcohol-preferring (P), Marchigian Sardinian (msP), high-alcohol-drinking (HAD), Fawn-Hooded (FH) rats were allowed to drink alcohol or water voluntarily to establish baseline levels. Pure compounds (puerarin, daidzin, daidzein or analogs) isolated from kudzu, extracts from HPE or ibogaine and its analog were given by either intraperitoneal or oral administration. After acute administration, all agents dose-dependently reduced alcohol intake with minimal effects on food intake. Puerarin and HPE were also effective following chronic treatment. Overall, it is clear that pure compounds (daidzin, puerarin), extracts from St. John's wort, ibogaine and an ibogaine analog suppress alcohol intake in animal models of excessive drinking with minimal effects on other appetitive behaviors. Although the true mechanisms of action of these compounds on alcohol intake are not fully understood, with the current information, it appears that these compounds exert their effects by modulating several neuronal systems implicated in drinking behavior. However, their role in the future of pharmacotherapy for alcoholism will depend upon the outcome of carefully conducted clinical trials.

Keywords: Kudzu; St. John's wort; Daidzin; Puerarin; Alcohol-preferring rats; Alcohol intake; Ibogaine; Ibogaine analog; Pharmacotherapy

1. Introduction

Alcohol dependency is a major health and socioeconomic problem throughout the world. Despite great progress made in the field in the past two decades, the development of suitable medications for the treatment of alcohol dependency remains a challenging goal for alcohol research. It is widely accepted that alcoholism is a complex heterogeneous disorder. Consequently, it is unlikely that existing pharmacological tools such as naltrexone (approved by FDA in 1994) and acamprosate (used in Europe) will be efficacious in every individual. Medical plants have been used for the treatment of alcohol dependency in China for centuries, but have only recently attracted the attention of western scientists. Recently, extracts of St. John's wort which have traditionally been used to treat mild to moderate depression, have drawn interest as potential antidipsotropic agents. The present communication provides a review of promising plants that have been shown to be effective in reducing alcohol intake in genetic animal models of human alcoholism. These models include St. John's wort, kudzu isoflavonoids, ibogaine and a nontoxic ibogaine analog.

2. St. John's wort

Extracts of the common plant *Hypericum perforatum* L. (HPE; St. John's wort) have been successfully used for the treatment of mild to moderate depression since ancient times. Recently, the antidepressant effect of HPE has been investigated in controlled clinical studies (Ernst, 1995; Linde et al., 1996; Volz, 1997; Laakmann et al., 1998; Melchart, 1996; Nordfors and Hartvig, 1997; Whiskey et al., 2001; Hypericum Depression Trial Study Group, 2002) as well as in laboratory animals (Butterweck et al., 1997; Nathan, 1999; Gambarana et al., 1999; Perfumi et al., 1999; Panocka et al., 2000). It has been suggested that the antidepressant effects of HPE might be mediated by increases in brain levels of serotonin (5-HT), dopamine (DA), norepinephrine or by stimulation of sigma and opioid

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receptors in the central nervous system (CNS) (Butterweck et al., 1997; Muller et al., 1997; Panocka et al., 2000).

Several reports indicate comorbidity between depression and alcohol abuse (Grant and Harford, 1995; Markou et al., 1998; Merikangas et al., 1998; Neighbors et al., 1992; Swensden et al., 1998), and there are data suggesting a relationship between high alcohol intake and a depression-like condition in some lines of alcohol-preferring rats. This has been reported in selectively bred alcohol-preferring AA rats (Kiinama et al., 1991; Viglinskaya et al., 1995), in the Fawn-Hooded (FH) rats (Overstreet et al., 1992; Rezvani et al., 2002) and in Sardinian (sP) and Marchigian Sardinian (msP) alcohol-preferring rats (Ciccocioppo et al., 1999). In the last two strains of rats, voluntary alcohol drinking or intragastric alcohol administration markedly reduced the immobility score in the forced swimming test. The antidepressant-like action of alcohol was not observed in alcohol-nonpreferring rats (Ciccocioppo et al., 1999).

These findings raise the questions of whether the high alcohol preference and intake of these strains of rats might be somehow related to the antidepressant-like action of alcohol, and whether antidepressant drugs in these rats might be able to reduce alcohol consumption. Interestingly, alcoholism and depression are known to have some common neurochemical substrates (Markou et al., 1998). For instance, it has been speculated that the pathophysiology of alcoholism and depression might involve preexisting low brain 5-HT levels that are increased transiently by alcohol consumption (Ballenger et al., 1979). Serotonergic compounds have been shown to reduce pathologic drinking in experimental animals (McBride et al., 1993; Murphy et al., 1988; Rezvani et al., 1991; Rezvani and Grady, 1994) and in heavy drinkers (Naranjo et al., 1990) and alleviate the symptoms of depressive disorders (Meltzer, 1990; Maes and Meltzer, 1995).

Because of this similarity in the pathogenesis of depression and alcoholism and in relation to the antidepressant properties of HPE, it has been hypothesized that HPE might also reduce voluntary alcohol intake in alcohol-preferring rats. In this section, we will review the findings obtained by different investigators concerning the effect of HPE on alcohol intake in alcohol-preferring rats.

2.1. Acute effect of HPE on voluntary alcohol intake in different strains of alcohol-preferring rats

The effects of HPE on voluntary alcohol intake have been studied by different laboratories in different strains of genetically selected alcohol-preferring rats: the FH rats, the high-alcohol-drinking (HAD) rats, the msP rats, and the cAA rats (Rezvani et al., 1999; Perfumi et al., 1999, 2001; De Vry et al., 1999; Panocka et al., 2000).

2.1.1. FH and HAD rats

The effect on alcohol intake of a methanolic HPE (LI 160, batch no. 970201 provided by Lecthwer Pharma, Berlin) has been evaluated (Rezvani et al., 1999). The extract contained 0.22% total hypericin (sum of hypericin and pseudohypericin) and 4.05% of hyperforin. It was shown that a single oral administration of different doses of this methanolic HPE significantly attenuated 10% alcohol intake, offered during the entire day, in freely feeding and drinking FH and HAD rats.

In HAD rats, a statistically significant reduction of alcohol drinking was obtained at the dose of 400 mg/kg, given by intragastric gavage; the dose of 600 mg/kg almost completely suppressed alcohol drinking in the first 6 h after HPE administration. In FH rats, a statistically significant reduction of the 6-h alcohol intake was obtained in response to 200 mg/kg, but the intensity of the attenuation of alcohol intake at higher doses was lower than in HAD rats. The attenuation of alcohol intake at 24 h after HPE administration was markedly reduced but remained statistically significant at the doses of 400 and 600 mg/kg in HAD, and at the dose of 800 mg/kg in FH rats (Rezvani et al., 1999).

There was a trend for water intake to increase. The combination of a significant reduction in alcohol intake and a moderate increase in water intake led to a significant reduction in alcohol preference. Acute oral administration of the HPE did not significantly influence food intake in FH rats, but the highest doses tested reduced food intake in HAD rats (Rezvani et al., 1999). Although this reduction in food intake was statistically significant, it was smaller than that for alcohol intake (71% and 93% reduction in alcohol intake from 3-day baseline vs. 20% and 27% reduction in food intake from 3-day baseline).

Alcohol-preferring rats, such as P and FH rats, exhibit rebound increases in alcohol intake when periodically withdrawn from their unlimited access to alcohol (Sinclair and Li, 1989; Rezvani et al., 2002). The enhanced intake of alcohol after alcohol withdrawal can be diminished with anticraving drugs. It has been demonstrated that one single oral dose (600 mg/kg) of HPE, but not vehicle, significantly blocked the enhanced alcohol intake seen in FH rats after 24-h alcohol deprivation. When HPE was compared with an oral dose of 25 mg/kg naltrexone in this paradigm, HPE was more potent in preventing the alcohol-deprivation effect, an animal model of relapse (Rezvani et al., 1999; Overstreet et al., 2003a).

2.1.2. msP rats

A pronounced attenuation of alcohol intake following HPE administration has been consistently observed in several studies carried out in msP rats (Perfumi et al., 1999, 2001; Panocka et al., 2000). These rats were derived from sP rats of the 13th generation (Colombo, 1997), provided by the Department of Neurosciences of the University of Cagliari (Italy), and then raised for additional 38 generations in the Department of Pharmacological Sciences and Experimental Medicine of the University of Camerino (Italy). Two extracts provided by Indena (Milan, Italy) were tested in these rats: the first extract (HPE1) was a methanolic extract with 3.8% hyperforin and 0.3% hypericin

comparable to those in the extract used in the FH and HAD rats. The second was a CO_2 extract (HPE2) containing 24.33% hyperforin and 0.03% hypericin. The two extracts were given by intragastric route through a polyethylene catheter (PE-50, Clay Adams) permanently implanted into the stomach. The IG polyethylene catheter was adopted for extract administration to avoid any possible disturbance to the animal.

HPE1 markedly reduced the voluntary intake of 10% alcohol, offered for 2 h/day at the beginning of the dark phase of the light cycle, in freely feeding and drinking rats. The effect was statistically significant with 125 mg/kg. It was also demonstrated that the intensity of the effect in a 2-h intake test in msP rats was influenced by the interval between the intragastric administration and the access to alcohol. The maximum effect on alcohol intake was observed when at least 1 h was allowed between HPE administration and the intake test. The effect of HPE1 was highly selective. Locomotor activity and food intake during the 2-h access to alcohol were not modified.

The reduction of alcohol intake was not accompanied by an increase in water intake. Water intake in msP rats is always very low. Apparently, the 2-h intake of alcohol in freely drinking rats has no homeostatic relevance in terms of fluid balance and its reduction does not need to be compensated in the short term. However, when rats were induced to drink water by 16-h water deprivation, HPE1 did not significantly modify water intake. Thus, the effect on alcohol intake appears to be selective.

In another set of experiments, the effect of HPE2, an extract much richer in hyperforin, was tested in msP rats. While the threshold dose for HPE1 was 125 mg/kg, the attenuation of alcohol intake was statistically significant in response to 15 mg/kg of HPE2; thus, the latter extract inhibited alcohol intake more potently than the former. The higher potency of HPE2 paralleled the hyperforin content, suggesting that hyperforin may have an important role in reducing alcohol intake. Food intake in the 2-h access to alcohol was not affected by doses that reduced alcohol intake. This is an interesting finding, because the reduction in food intake can be regarded as an adverse side effect in chronic alcoholics who are frequently malnourished. When msP rats were offered 0.2% saccharin 2 h/day, the intake of the sweet solution was not affected by the intragastric administration of HPE2, even at the highest dose used in alcohol intake experiments. Thus, it appears that the effect of HPE2 on alcohol intake is highly selective.

2.1.3. cAA rats

cAA rats have been derived from alcohol-accepting AA rats (Helsinki, Finland) in Cologne, Germany. Similar to AA rats, these rats drink significant amounts of alcohol and exhibit a high preference for alcohol. The HPE employed, Ze 117 (Remotiv, Zeller, Romanshorn, Switzerland), was administered by intraperitoneal injection in freely feeding and drinking rats just before the beginning of a daily 12-h access to 10% alcohol. This extract significantly reduced alcohol drinking at doses of 20 and 40 mg/kg. The dose of 40 mg/kg also significantly reduced alcohol preference and food intake, whereas the dose of 20 mg/kg modified neither alcohol preference, nor food intake, nor total fluid intake. Thus, HPE exerted a rather selective effect on alcohol intake also in cAA rats (De Vry et al., 1999).

2.2. Chronic effects of HPE on voluntary alcohol intake in different strains of alcohol-preferring rats

Chronic treatments with HPE have been carried out in both FH and msP rats. In FH rats, repeated administration of the methanolic HPE (LI 160, containing 0.22% total hypericin and 4.05% hyperforin) for 15 consecutive days significantly reduced alcohol intake at 24 h without development of tolerance (Rezvani et al., 1999). This is an important finding because tolerance develops to suppressant effect of other drugs, including naltrexone, on alcohol intake (Rezvani et al., 1992; Overstreet et al., 1999b) but not HPE.

Chronic treatment with HPE2 has been carried out also in msP rats with 2 h/day access to alcohol. The extract was daily administered by intragastric route 1 h before access to alcohol. The attenuation of alcohol intake was observed since the first day of treatment and was maintained for the duration of the treatment (12 consecutive days). When it was discontinued for a day (Day 8) alcohol intake returned to normal baseline levels. After the termination of the treatment, rats promptly resumed normal alcohol intake (Perfumi et al., unpublished data). Absence of tolerance has been also reported in regard to the antidepressant-like effect of HPE in the forced swimming test (Winterhoff et al., 1995).

These findings suggest that tolerance to the suppressant effect of the extract on alcohol intake does not develop during chronic treatment with these extracts. The fact that the animals resume their normal alcohol intake after termination of the treatment suggest that HPE does not induce conditioned aversion to alcohol. These findings also suggest that the treatment with HPE must be continued indefinitely to achieve long-term suppression of alcohol intake.

2.3. Synergism with opioid receptor antagonists

Opioid receptor antagonists, such as naloxone and naltrexone, are known to reduce alcohol intake in rats and in humans (Overstreet et al., 1999a,b,c). A recent study in msP rats evaluated the effect on alcohol intake of the combined administration of HPE2 and of opioid receptor antagonists. When naloxone, 1 mg/kg, or naltrexone, 0.5 mg/kg, were given before different intragastric doses of HP2, the attenuation of alcohol intake was more pronounced than that observed following HPE2 alone (Perfumi et al., 2003). The effect of the combined treatment was behaviorally selective, because food or saccharin intake were not reduced.

These results suggest a synergistic action of opioid receptor antagonists and HPE2 in eliciting a pronounced and selective reduction of alcohol intake in msP rats. In addition, these findings support once more the validity of combination pharmacotherapy in the treatment of excessive drinking (Rezvani et al., 2000) and stimulate further studies to understand the mechanisms responsible for the synergism observed in the present study.

2.4. Effect of HPE on blood alcohol levels

Drugs that suppress alcohol intake may do so by one of two broad mechanisms: peripherally, by altering alcohol metabolism (e.g., disulfiram), or centrally, by reducing the rewarding effects of alcohol (e.g., naltrexone). Compounds that influence alcohol metabolism and act like disulfiram might not be desirable because of their severe side effects. Thus, it is crucial to determine if the attenuating effects of HPE on alcohol intake are centrally or peripherally mediated. The effect of HPE on blood alcohol levels (BAL) was investigated in msP rats (Perfumi et al., 1999, 2001). Administration of 125 or 250 mg/kg HPE1, which produced a marked reduction in alcohol intake, did not affect BAL in msP rats. Blood acetaldehyde levels also did not change in response to HPE1 administration, thus excluding a possible disulfiram-like effect (Perfumi et al., 2001). However, the results obtained with HPE2 were different, in that this extract reduced BAL at 31 mg/kg or higher doses, whereas the dose of 15 mg/kg reduced alcohol intake, but did not modify BAL (Perfumi et al., 2001). These findings suggest that reduction of alcohol intake and reduction of BAL may be independent effects. Based on these findings, the hypothesis has been put forward that the effect on alcohol intake might be the consequence of central effects, whereas the effect on BAL might be due to influence on alcohol absorption and to greater degradation of alcohol by the gastric alcohol dehydrogenase. The hypothesis that the two effects may be independent also relies on the assumption that reduction of BAL should not decrease, but rather increase, alcohol consumption in an attempt to obtain the expected effects of alcohol. A similar dual action has been observed for isoflavonoid daidzin (Xie et al., 1994; see Section 2.5).

The relationship between the effects on alcohol intake and that on BAL remains to be elucidated; however, it is interesting to note that HPE, while reducing alcohol intake, may also lower BAL levels, thus reducing the potential toxic effects of alcohol.

2.5. Active principles

HPE contains a variety of biologically active compounds, including naphtodianthrones (hypericin and pseudohypericin), fluoroglucynol derivatives (hyperforin, adhyperforin), several flavonol glycosides (quercetin, hyperoside or hyperin, rutin, isoquercitrin), biflavones (amentoflavone), phenylpropanes (chlorogenic acid, caffeic acid), proanthocyanidins, tannins, xanthones and certain amino acids, such as GABA (Nahrstedt and Butterweck, 1997; Barnes et al., 2001; Jensen et al., 2001).

Hypericin and hyperforin have been proposed to mediate several effects of HPE. A large body of evidence suggests that hyperforin may represent the major component responsible for the antidepressant effect of HPE (Bhattacharya et al., 1998; Chatterjee et al., 1998; Laakmann et al., 1998; Muller et al., 1998, 2001; Kaehler et al., 1999; Singer et al., 1999; Vormfelde and Poser, 2000; Di Carlo et al., 2001).

The studies carried out in msP rats have shown that HPE2 is about eight times more potent than HPE1 in inhibiting alcohol intake in msP rats (Perfumi et al., 2001). HPE2 has 24.33% hyperforin and very low hypericin content, whereas HPE1 contains 3.8% hyperforin and 0.3% hypericin. Thus, the potency of the two extracts in reducing alcohol intake parallels the hyperforin content, not the hypericin content. These observations suggest that hyperforin might have a greater role than hypericin in attenuating alcohol intake. Hyperforin is readily bioavailable following oral administration, is able to cross the blood–brain barrier (Ostrowski et al., 1988), influences several neurochemical systems in the brain and is responsible for behavioural effects of HPE (Bhattacharya et al., 1998; Chatterjee et al., 1998, 1999; Laakmann et al., 1998; Muller et al., 1998; Kaehler et al., 1999; Singer et al., 1999). However, it cannot be excluded that the effects of HPE on alcohol intake may result from the combined action of several components of the extract.

Studies are under way to prepare pure hyperforin salts or derivatives endowed with sufficient water solubility to evaluate their effect on alcohol intake in msP rats. It will be interesting to evaluate the effect of these hyperforin derivatives and to compare their effect with that of other active compounds contained in HPE.

2.6. Interactions with neurochemical systems

Several studies suggest that extracts from St. John's wort increase serotonergic neurotransmission (Perovic and Muller, 1995; Cott et al., 1997; Muller et al., 1997; Nahrstedt and Butterweck, 1997; Calapai et al., 1999; Kaehler et al., 1999; Neary et al., 1999) by reducing 5-HT reuptake and inhibiting monoamine oxidase (MAO) activity (Cott et al., 1997; Nahrstedt and Butterweck, 1997). It is also noteworthy that components of HPE show remarkable affinity for 5-HT_{1A} receptors (Cott et al., 1997) and that HPE-treated rats have been reported to exhibit an increased number of 5-HT_{1A} and 5-HT_2 receptors (Teufel-Maye and Gleitz, 1997). All these effects can influence 5-HT neurotransmission.

HPE has been shown to reduce not only 5-HT reuptake, but also noradrenaline, DA and L-glutamate reuptake (Muller et al., 1997; Chatterjee et al., 1998). Butterweck et al. (1997) showed that the effects of HPE in the forced swimming test may be at least in part mediated by activation

not only of dopaminergic but also of opioid mechanisms. Hyperforin has also been reported to inhibit the reuptake of 5-HT, DA and noradrenaline, with IC_{50} of about 50–100 ng/ml, and L-glutamate, with IC_{50} of about 500 ng/ml (Muller et al., 1998; Bennett et al., 1998; Chatterjee et al., 1998; Kaehler et al., 1999). Cott et al. (1997) also reported that hypericin shows affinity for the NMDA receptor in the micromolar range.

Moreover, HPE and the active constituent hyperforin have been shown to act as potent inhibitors of GABA reuptake (Dimpfel et al., 1998; Wonnemann et al., 2000; Nathan, 2001). In addition, a recent study has shown that hyperforin facilitates GABA release from synaptosomes (Chatterjee et al., 2001). Binding studies have demonstrated that HPE exhibits high affinity for the $GABA_B$ receptors and moderate affinity for $GABA_A$ receptors (Cott et al., 1997; Gobbi et al., 1999). At a functional level, GABA-mimetic properties of HPE are indicated by their anxiolytic effects, which are blocked by pretreatment with the benzodiazepine (BZD) antagonist flumazenil (Kumar et al., 2000; Vandenbogaerde et al., 2000). A large body of evidence shows that GABAergic mechanisms modulate the motivational properties of alcohol and influence alcohol intake in rats and humans (Boyle et al., 1993; Korpi, 1994; Tomkins and Fletcher, 1996; Nowak et al., 1998; McBride and Li, 1998; Koob et al., 1998; Chester and Cunningham, 1999; Colombo et al., 2000; Addolorato et al., 2000; Malatynska et al., 2001).

Hypericin, one of the most important biologically active component of HPE (Butterweck et al., 1998), has been reported to bind with high affinity to sigma receptors (Raffa, 1998). These receptors may be involved in the relief of behavioral despair in the forced swimming test (Matsuno et al., 1996). Recently, effects of chronic treatment with St. John's wort on neurochemical markers of 5-HT, DA and opioid systems in mesolimbic regions of the FH rats were investigated by quantitative autoradigraphy. After 10 days of consecutive treatment, St. John's wort significantly increased ^{3}[H]citalopram binding to 5-HT transporters in multiple mesolimbic regions. On the other hand, treatment with St. John's wort resulted in an increased binding of ^{3}[H]mazindole in the olfactory tubercle and a decreased binding in the ventral tegmental area. In addition, St. John's wort also resulted in differential modulation of the binding properties of 5-HT_{1A}, 5-HT_{2A} and μ-opioid receptors in a region-specific manner (Chen et al., 2003).

2.7. Possible mechanisms of action of St. John's wort on alcohol intake

The mechanism of action for the effect of HPE on alcohol intake is essentially unknown. At a neurochemical level, it has been investigated whether the effect of HPE might be mediated by increased serotonergic or GABAergic transmission, or sigma receptors (Panocka et al., 2000; Perfumi et al., 2001, 2002, 2003). However, treatment with 5,7-dihydroxytryptamine (5,7-DHT), or sigma or GABA receptor antagonists did not modify the effect of HPE on alcohol consumption, although the first two treatments were able to reduce the antidepressant-like effect of the HPE in the forced swimming test.

More recently, the effect of the opioid receptor antagonists on the effect of HPE2 on alcohol intake has been investigated in msP rats. While opiate receptor antagonists have been reported to reduce the antidepressant-like effect of HPE in the forced swimming test (Butterweck et al., 1997), they did not reduce but indeed increased the effect of HPE2 on alcohol intake (Perfumi et al., 2002, 2003).

Further studies are required to evaluate the possible involvement of other neurochemical systems, such as the dopaminergic or glutamatergic systems, in the effect of HPE on alcohol intake. Interest for the dopaminergic system has been emphasized by a recent study showing that hyperforin has good affinity at dopaminergic D1 receptors (Butterweck et al., 2002). However, in relation to the ability of the variety of active compounds in HPE to influence many neurochemical systems, it may be speculated that the effect of HPE on alcohol intake might be due to the simultaneous activation of several neurochemical systems involved in alcohol intake regulation.

At a motivational level, the information is still incomplete. HPE has not been investigated in place or taste conditioning studies to evaluate whether it might exhibit rewarding or aversive properties. HPE exhibits antidepressant-like effect that might substitute, at least in some alcohol-preferring rats, for the effects of alcohol. However, it appears that the antidepressant-like effect and the effect on alcohol intake of HPE2 in msP rats are two independent effects. HPE2 also has been shown to exert anxiolytic-like effects in rats (Vandenbogaerde et al., 2000; Flausino et al., 2002), which may substitute, at least in part, for the effects on alcohol in alcohol-preferring rats. However, different strains of rats have been used for alcohol intake studies and for studies on the anxiolytic effect; therefore, further investigations are needed to evaluate both effects in the same strain of alcohol-preferring rats.

Because the crude extracts employed so far have been given only by the intragastric or intraperitoneal route, the site of action for the effect of HPE on alcohol intake remains to be determined. The administration of pure hyperforin or other proven active compounds into the specific regions of the CNS is required to assess whether the effect is evoked at a central or peripheral site.

2.8. Conclusions

The preclinical studies with several strains of alcohol preferring rats show that an acute oral administration of St. John's wort extracts can significantly reduce voluntary alcohol intake. Further, tolerance to this effect of extracts does not develop after chronic treatment. Although HPE has

been used since antiquity for the treatment of mild to moderate depression, its effect on alcohol consumption in human alcoholics has not been evaluated in detail. To the best of our knowledge, only one study has suggested the beneficial effect of St. John's wort for the treatment of alcoholic patients (Krylov and Ibatov, 1993). Although the mechanism of action of the extracts of St. John's wort on alcohol intake is not fully understood, the ability of HPE to affect serotonergic, dopaminergic and opioidergic systems in mesolimbic regions in the CNS, directly or indirectly, might help to explain the efficacy of HPE in the treatment of mild to moderate depression and alcoholism.

3. Kudzu isoflavonoids

Recently, it has been demonstrated that isoflavonoids isolated from the kudzu plant are effective in reducing alcohol intake. Keung and coworkers reported that daidzin and daidzein were the active herbal components isolated from *Radix pueraria* (RP; kudzu) that suppressed alcohol intake in Syrian golden hamsters (Keung and Vallee, 1993a,b; Keung et al., 1995). Furthermore, daidzin differs from disulfiram in its selective and reversible inhibition of ALDH-1 (Keung and Vallee, 1993a). Daidzin also decreases BAL and shortens sleep time induced by alcohol (Xie et al., 1994). This effect has been attributed to the antioxidant properties of daidzin, as vitamin E is also effective (Xie et al., 1994). These findings, together with reports of the effective reduction of drinking by kudzu extract NPI-028 (Overstreet et al., 1996a,b, 1998), provide a scientific basis for the traditional use of kudzu in the treatment of alcohol intoxication in China. The Chinese herbal medicine XJL (NPI-028) has long been used to reduce the inebriation that results from alcohol consumption. NPI-028 consists of several Chinese herbal plants including kudzu (*Pueraria lobata*), which was recorded in an ancient Chinese materia medica entitled Ben Cho Gang Mu and has long been used to lessen alcohol intoxication (Li Ben Cho Gang Mu, 1560–1566).

Results of initial studies demonstrated that NPI-028 could significantly suppress alcohol drinking (− 40%) in a 24-h free-choice alcohol drinking study using two different strains of alcohol-preferring rats. Furthermore, in a scheduled limited-access paradigm, NPI-028 produced a dose-dependent reduction in alcohol drinking. At 0.5 and 1.5 g/kg (intraperitoneal injection), it reduced alcohol intake by 50% and 100%, respectively. In both experiments, food and water intakes were not affected (Overstreet et al., 1996a,b). It was also demonstrated that NPI-028 was effective at lower doses in reducing alcohol intake in alcohol-preferring African green vervet monkeys (Overstreet et al., 1998).

Following these studies with NPI-028, comprehensive fractionation studies of kudzu, a major herbal component in NPI-028 was conducted. A total of seven compounds were obtained. It was shown that the effective doses for these purified components were 5- to 10-fold lower than the dose of NPI-028 itself. One common feature of these active components is a hydroxylated isoflavone, with or without a glucose unit attached. The compounds with a glucose moiety, such as daidzin and puerarin, are more potent than the corresponding aglycone (Overstreet et al., 2002b). It is conceivable that the sugar moiety enhances the solubility of the compound and facilitates its absorption and excretion. The sugar moiety in puerarin and its analogs is attached to the aglycone through a carbon–carbon bond, which is more stable to enzymatic hydrolysis and metabolic activation than an ordinary carbon–oxygen bond such as in daidzin (Lee et al., 1989). The present section will first review recent studies on the efficacy of daidzin or puerarin in suppressing alcohol intake and then examine several reports that have directly compared daidzin with puerarin.

3.1. Daidzin

Daidzin, a major active principle of an ancient Chinese herbal treatment (RP) for alcohol addiction, was first shown to suppress alcohol intake in alcohol-preferring Syrian golden hamsters (Keung and Vallee, 1993a). Since then, the suppression of alcohol intake by daidzin and RP extracts have been observed in all alcohol-drinking animals tested to date (Heyman et al., 1996; Lin et al., 1996; Overstreet et al., 1996a, 1998). The mechanism by which daidzin suppresses alcohol intake is not fully understood, but there are several intriguing hypotheses.

Daidzin has been shown to inhibit liver mitochondrial aldehyde dehydrogenase (ALDH-2) and it may suppress alcohol intake by alcohol sensitization (Keung and Vallee, 1993b). However, a later study demonstrated that daidzin did not affect the overall alcohol and acetaldehyde metabolism at doses that effectively suppressed hamster alcohol intake (Keung et al., 1995). These conflicting results were resolved when a cytosolic ALDH isozyme was found in hamster liver; this isozyme catalyzes acetaldehyde oxidation efficiently and is not inhibited by daidzin (Klyosov et al., 1996). Therefore, daidzin does not appear to suppress hamster alcohol intake in the same manner as the classic ALDH inhibitors, disulfiram and calcium carbimide. Daidzin may act by modulating the activity of an as-yet-undefined physiological pathway catalyzed by ALDH-2.

ALDH-2 could be involved in monoamine metabolism, catalyzing the second step of 5-HT or DA metabolism (Tank et al., 1981). Recently, it has been shown that daidzin inhibited the conversion of 5-HT to 5-hydroxyindole-3-acetic acid (5-HIAA) and DA to 3,4-dihydroxyphenylacetic acid (DOPAC) in isolated hamster and rat liver mitochondria (Keung and Vallee, 1998). Inhibition was accompanied by a concomitant increase in 5-hydroxyindole-3-acetaldehyde (5-HIAL) and 3,4-dihydroxyphenylacetaldehyde (DOPAL) accumulation (Keung and Vallee, 1998). Correlation studies using a series of daidzin analogs revealed a positive correlation between their potencies in suppressing alcohol intake and increasing 5-HIAL accumulation during

5-HT metabolism in isolated hamster liver mitochondria. Daidzin analogs that inhibited ALDH-2 potently but had little or no effect on MAO were the most effective in suppressing alcohol intake, whereas those that also inhibited MAO were not. It was therefore hypothesized that the mitochondrial MAO-ALDH pathway is a potential site of action for daidzin and that one or more biogenic aldehydes derived from the action of MAO, such as 5-HIAL, may be important in suppressing alcohol intake in these animals (Rooke et al., 2000).

In mammalian tissues, 5-HIAL is mainly oxidized to 5-HIAA. Small portions of it can be reduced to 5-hydroxytryptophol (5-HTOL) and condensed with biogenic amines, proteins and lipids to form various condensation products (CPs) (Alivisatos and Tabakoff, 1973). Daidzin, by inhibiting ALDH-2, can in principle divert part of the 5-HT metabolic flux from the major, oxidative pathway to the minor, alternative ones. Volitional alcohol consumption has been shown to affect 5-HT metabolism in humans (Davis et al., 1967) and laboratory rodents (Keung et al., 2000). Therefore, its effects on 5-HT metabolism in the tissue slices were also examined for comparison.

Both hamster and rat liver slice preparations metabolized 5-HT efficiently. However, the metabolic fate of 5-HT in the liver of the two animal species differed significantly. In the hamster liver, about 85% of the added 5-HT was metabolized to 5-HIAA, whereas in the rat liver, only 56% of the substrate was metabolized to 5-HIAA. Nonetheless, in both cases, daidzin inhibited 5-HIAA formation and diverted significant part of their 5-HT metabolic flux to the alternative pathways, forming 5-HTOL and unidentified CPs. At 15 μM, the highest concentration tested, daidzin decreased 5-HIAA formation by about 25% but increased that of 5-HTOL and CPs by >200% and >100%, respectively. Interestingly, like daidzin, alcohol also decreased 5-HIAA but increased 5-HTOL and CPs formation in hamster and rat liver slices. The effect of alcohol on 5-HTOL formation appeared to be specific and was not due to its general effect on NADH regeneration because another NADH-regenerating substrate, lactate, at a concentration as high as 10 mM failed to stimulate the 5-HTOL pathway in both liver slice preparations (Keung and Vallee, 1998; Keung et al., 2000).

While the physiological implication of shifting 5-HT metabolism from the major, oxidative pathway to the minor, alternative pathways is unknown at this time, the CPs of biogenic aldehydes have been shown to modulate alcohol drinking in laboratory animals—the "biogenic aldehyde hypothesis" (Deitrich and Erwin, 1980). The fact that the golden hamsters, as opposed to the rats, consume large amounts of alcohol may stem from the fact that the hamsters have a relative low MAO-to-ALDH-2 activity ratio. As a result, substantially less of the 5-HT in golden hamsters is channeled to the alternative pathways. This may create a "deficient state," and alcohol drinking may be a behavior that the hamsters have adopted to correct for such deficiency (Keung et al., 2000).

Similar to the liver, the minor pathways of 5-HT metabolism in the rat brain are also more active than those in its hamster counterpart. As a result, substantially larger portions of its 5-HT metabolites are CPs. Further, no 5-HTOL was detected in brain preparations, consistent with the fact that ADH, required for the reduction of 5-HIAL to 5-HTOL, is absent in the brain (Alivisatos and Tabakoff, 1973). Interestingly, 5-HT metabolism in both hamster and rat brain preparations were neither affected by daidzin nor alcohol. Tissue distribution studies indicated that daidzin given at doses that suppress hamster alcohol intake accumulated in the liver and was not detected in the brain (Keung et al., 2000). Thus, the fact that daidzin did not affect brain 5-HT metabolism could be due to the following: (i) It does not enter the brain slices and/or (ii) its target enzyme ALDH-2 is either absent or plays a very minor role in 5-HT metabolism in the brain (Beedham et al., 1995). Unlike daidzin, alcohol is freely distributed in the body after ingestion. Therefore, the fact that alcohol had no effect on brain 5-HT metabolism can be explained as follows: (i) alcohol's effects on liver 5-HT metabolism were mediated by its metabolic intermediate acetaldehyde, which acted as a competing substrate of 5-HIAL for ALDH-2 and (ii) the brain has no class I ADH isozyme, which is required for the conversion of alcohol to acetaldehyde. In this context, it might be of interest to revisit the idea that acetaldehyde rather than alcohol is a stronger reinforcing agent in the CNS (Brown et al., 1979). In summary, it appears that daidzin may suppress alcohol intake in rodents by inhibiting the conversion of 5-HT to 5-HIAA and DA to DOPAC in the mitochondria (Keung and Vallee, 1998).

3.2. Puerarin

Puerarin is the most concentrated isoflavonoid in kudzu. Although it is not as potent as daidzin (Overstreet et al., 1996b), the sugar moiety is attached to the carbon molecule instead of the oxygen, leading to a more stable compound than daidzin. The puerarin used in these studies was isolated from kudzu by Natural Pharmacia International (Belmont, MA), using countercurrent chromatography technique (Lee et al., 1989).

After acute intraperitoneal administration, puerarin reduced alcohol intake selectively (Overstreet et al., 1996b, 1997; Lee et al., 1999). Food intake was rarely affected and water intake, when affected, tended to increase. At doses used in the alcohol intake studies, puerarin did not affect general activity or social interaction behavior (Overstreet et al., 2002a). Thus, puerarin has relatively selective effects on alcohol intake. Interestingly, reduction of alcohol intake was observed in all three strains tested: the FH (Overstreet et al., 1996b, 1997), HAD (Overstreet et al., 1997) and P rats (Overstreet et al., 2001).

Puerarin or extracts of kudzu enriched in puerarin have also been shown to reduce alcohol intake by gavage (Lee et al., 1999; Overstreet et al., 1999a). Interestingly, the effect-

ive doses were approximately the same for the intraperitoneal and oral routes. It has also been shown that puerarin may be self-administered by vervet monkeys or P rats by adding it to a highly palatable saccharin (0.1%) solution (Overstreet et al., 1999c, 2002b). The most recent study allowed the P rats to self-administer puerarin in a saccharin solution for 28 consecutive days, with a resulting 50% decrease in alcohol intake (Overstreet et al., 2002b). The fact that puerarin was effective after oral administration for at least 28 days is particularly encouraging because rats develop tolerance to the suppressing effects of opiate antagonists on alcohol intake (Cowen et al., 1999; Hyytia et al., 1999; Overstreet et al., 1999b).

The beneficial effects of puerarin on alcohol intake in alcohol-preferring rats and monkeys suggest that puerarin potential as an anticraving agent. However, kudzu extracts were not traditionally used for this purpose. Instead, kudzu extracts were traditionally used in China to relieve intoxication and hangover from excessive alcohol drinking. Xie et al. (1994) have provided support for the intoxication relief hypothesis by demonstrating that oral administration of isoflavones before oral administration of alcohol led to lower BAL due to inhibition of the passage of alcohol across gut membranes.

3.2.1. Anxiolytic effects of puerarin

Because alcohol hangover and withdrawal are associated with anxiety and kudzu root extract traditionally has been used to alleviate hangover, it was hypothesized that puerarin may reduce anxiety associated with alcohol withdrawal in rats. The anxiety-related behavior in rats withdrawn from chronic exposure to alcohol has been well documented (e.g., Criswell and Breese, 1992; File et al., 1989; Kampov-Polevoy et al., 2000; Knapp et al., 2000; Moy et al., 1997, 2000). After 15 days exposure to an alcohol (7%) diet, rats were withdrawn for 5 h and tested for anxiety-like behavior in the social interaction test. Puerarin (50 and 150 mg/kg) partially counteracted the reduction in social interaction behavior induced by alcohol withdrawal, as did flumazenil, a BZD antagonist, and SB242084, a 5-HT_{2C} antagonist (Overstreet et al., in press). Thus, puerarin might also be useful in counteracting some of the symptoms experienced by alcoholics during the detoxification phase of treatment.

The fact that BZD and 5-HT_{2C} antagonists also counteracted the diminished social interaction observed in alcohol withdrawn rats (Knapp et al., 2000) resulted in testing whether the anxiolytic effects of puerarin might be mediated by BZD or 5-HT_{2C} mechanisms. The BZD inverse agonist, DMCM, and the 5-HT_{2C} agonist, Ro 60 0175, induce anxiety-like behavior in the social interaction test (reduced social interaction). It was investigated whether puerarin would counteract these effects. Indeed, puerarin significantly increased social interaction behavior in the rats treated with DMCM or Ro 60 0175, suggesting that it might act as both BZD and 5-HT_{2C} antagonists (Overstreet et al., 2002a, in press). Puerarin did not modify the increases in chloride flux induced by the $GABA_A$ agonist, muscimol, indicating that it does not have agonist or partial agonist activity at the BZD receptor. Puerarin did reduce the potentiating effects of flunitrazepam, a BZD agonist, on muscimol-stimulated chloride flux, but only at the high dose of 100 μM. In contrast, the classical BZD antagonist flumazenil blocked the effect of flunitrazepam at 2 μM. Thus, puerarin appears to act as a weak antagonist at BZD receptors. To confirm these relationships, the effect of flumazenil and/or SB242084 on alcohol intake in P rats was tested. At doses 10- to 30-fold lower than the standard dose of puerarin (150 mg/kg), both compounds significantly reduced alcohol intake in the P rats (Overstreet, unpublished results, 2003b). Clearly, the involvement of BZD and 5-HT_{2C} receptors in the regulation of alcohol intake needs to be more systematically examined.

The dose of 150 mg/kg puerarin for alcohol-preferring rats would translate to 10.5 g for a 70-kg human, a very large dose. However, other data suggest that this simple calculation is too simple. For example, the standard dose for naltrexone in human alcoholics is 50 mg or approximately 0.71 mg/kg and it has been reported that a dose of 26 mg/kg is needed to suppress alcohol intake in rats over 24 h (Overstreet et al., 1999b). This ratio is about 37 and if this ratio is applied to puerarin, then the standard human dose would be 5.55 g. This is still a very high daily dose, even more than the typical dose of acamprosate. A more potent analog of puerarin might overcome this shortcoming.

The studies on the blocking effect of puerarin on the anxiety-like behavior induced by DMCM and the potentiation of muscimol-stimulated chloride flux by flunitrazepam clearly indicate that puerarin may be a weak BZD antagonist. Recently, it was confirmed that puerarin does not reduce [^{3}H]flunitrazepam binding until 100 μM (Overstreet et al., in press). This finding supports the conclusion that puerarin is a weak antagonist at the BZD receptor and replicates the finding of Shen et al. (1996). However, there are as yet no in vitro findings of the action of puerarin at the 5-HT_{2C} receptor, so we cannot conclusively state that puerarin is an antagonist at the 5-HT_{2C} receptor.

3.2.2. Clinical findings

Although kudzu extracts have been used for many centuries in China to relieve intoxication and hangover from excessive drinking, the authors are aware of only one published clinical study on kudzu (Shebeck and Rinbone, 2000). Recently, Shebeck and Rindone (2000) in a pilot study explored the effect of kudzu root extract on the drinking habits of patients with chronic alcoholism. Patients with the diagnosis of alcoholism were randomly assigned to receive either kudzu root extract 1.2 g twice daily or a matching placebo. Sobriety level and craving for alcohol were assessed on a visual analog scale. In this small patient population, kudzu root appeared to be no better than placebo in reducing the craving for alcohol or promoting sobriety. As the investigators have discussed it, the negative results could have been due to study design. Patients were asked to

complete the questionnaire on their own. It is likely that patients may not have completed the survey accurately. The significant withdrawal of subjects from the study resulted in a small sample size, which led to a diminished statistical power. "Based on these findings, firm conclusions on the efficacy of kudzu root are not justified, although our data suggest the compound to be ineffective" (Shebeck and Rindone, 2000). Further study of the effect of kudzu root extract on alcohol intake with a greater number of patients with or without psychotherapy and counseling may reveal new information on the effect of kudzu on drinking. Anecdotal reports from China and experimental studies in rats (Keyler et al., 2002) indicate that these herbal compounds have very low toxicity and they should, therefore, be tolerated well by human patients. One very motivated alcoholic took the complex herbal mixture (NPI-028) for 13 weeks. There was a reduction in her alcohol drinking from 12 beers a day to 0 and her craving rating was reduced by almost half after drinking the tea containing the NPI-028 (from 7 out of 10 to 4). All the evidence available to date indicates that puerarin or kudzu extracts are ready to be tested clinically.

3.3. Comparative studies

Two studies have directly compared the abilities of daidzin and puerarin to suppress alcohol intake. Lin et al. (1996) mixed daidzin, daidzein or puerarin in the food of female P rats and used a restricted food paradigm to insure that the rats received the right dosage of the isoflavones. All three compounds suppressed alcohol intake during the treatment period. However, daidzin was more effective than the other two (Lin et al., 1996). In another study, FH rats were injected intraperitoneally with selected doses of daidzin, daidzein and puerarin. Daidzin again was the most effective, whereas puerarin had a smaller but still significant suppressing effect and daidzein was ineffective. Thus, daidzin is more potent than puerarin. Because of its chemical structure, with the glucose moiety attached to the oxygen, daidzin is likely to be metabolized to daidzein, which appears to be less effective in rats (Overstreet et al., 1997). In addition, daidzin has phytoestrogenic activity (Farmakalidis et al., 1985), so it may not be safely injected in a chronic regimen. In contrast, puerarin does not act as a phytoestrogen and because the sugar moiety is attached to a carbon molecule, it is more resistant to metabolism. This feature no doubt accounts for the gradually greater suppression of alcohol intake in P rats that were chronically treated with puerarin (Overstreet et al., 2001, 2002a,b).

4. Ibogaine and ibogaine analog

Ibogaine is one of the principal indole alkaloids found in the root bark of the African shrub *Tabernanthe iboga* (Apocynaceae family) that grows in West Central Africa. It has been reported that the crude extracts of ibogaine cause a feeling of excitement, drunkenness, mental confusion and possibly hallucinations when taken in high doses. Ibogaine has been claimed to be effective in treating multiple forms of drug abuse, including morphine, cocaine, heroin and nicotine (Glick et al., 1991; 1996; Glick and Maisonneuve, 1998; Mash et al., 1998). Although not conclusive, it has been proposed that ibogaine exerts its anticraving effects by stimulating dopaminergic and serotonergic systems (Glick et al., 1991). Because both systems have been implicated in the regulation of alcohol intake (Rezvani et al., 1991, 2000), it was hypothesized that ibogaine and its nontoxic analog (18-methoxycoronaridine, or 18-MC) may reduce alcohol intake by modulating dopaminergic and serotonergic systems.

4.1. Ibogaine

Both acute and subchronic treatments were carried out with ibogaine. A single subcutaneous administration of different doses of ibogaine did not exert a significant effect on alcohol intake in FH rats. However, when ibogaine was injected intraperitoneally, it significantly attenuated alcohol intake and alcohol preference in FH, P and AA rats in a dose-dependent manner. Administration of 10, 30, and 60 mg/kg ibogaine ip induced 8%, 13% and 25% ($P<.05$) reduction in alcohol preference in AA rats. The corresponding values for FH and P rats were 20%, 26% and 51% ($P<.01$) and 22%, 39% ($P<.01$) and 63% ($P<.001$), respectively. The higher dose of 60 mg/kg ibogaine exerted a significant effect on all three strains but P rats were more affected (Rezvani et al., 1995). The food intake in FH and AA rats was not affected by intraperitoneal administration of ibogaine. However, food intake in P rats was reduced significantly by the administration of 10 and 60 mg/kg ibogaine. Similar to intraperitoneal injections, a single oral administration of 60 mg/kg into FH rats also significantly reduced (60%) alcohol intake and preference.

Subchronic administration of 60 mg/kg ibogaine into FH rats by gavage for five consecutive days significantly ($P<.0001$) and consistently reduced alcohol intake without the development of tolerance and a significant change on food and water intake. However, 5-day treatment is too short to draw a conclusion about the chronic effects of ibogaine and development of tolerance.

Possible effects of ibogaine on BAL have been studied in a group of alcohol-naïve FH rats. Adult male FH rats were injected intraperitoneally with either 60 mg/kg ibogaine or an equal volume of control vehicle and 15 min later with a dose of 2.5 g/kg alcohol (16% vol/vol) using a crossover design with a 1-week interval. Blood sample was drawn from the tip of the tail at 1, 3 and 5 h after alcohol injection for determination of BAL (Rezvani and Grady, 1994). Compared with control vehicle, it was found that a single injection (intraperitoneal) of a high dose of ibogaine into FH rats did not significantly affect BAL (Rezvani et al., 1995).

4.2. Ibogaine analog

Because ibogaine, at high doses, can be toxic and cause side effects that may limit its therapeutic applications, an attempt has been made to design an ibogaine analog with no toxicity but with the same inhibitory action on reinforcing drugs. 18-MC appears to be such an analog. 18-MC treatment has been shown to suppress morphine and cocaine self-administration in rodents, presumably by influencing the dopaminergic system in the nucleus accumbens (Glick et al., 1996). Because the dopaminergic system has been shown to be involved in the reinforcing property of alcohol and other drugs of abuse, the suppressant effects of this compound on intake of alcohol of male P rats were examined.

It was shown that a single injection (intraperitoneal) of 5, 20 or 40 mg/kg 18-MC significantly reduced alcohol intake and preference in a dose-dependent manner in P rats. Administration of 18-MC resulted in an overall increase in water intake ($P < .01$). Although a single dose of 5 or 20 mg/kg 18-MC did not exert a significant effect on food intake, an injection of 40 mg/kg 18-MC significantly reduced food consumption (Rezvani et al., 1997).

4.3. Possible mechanisms of action of ibogaine and its analog

Several neuronal mechanisms may be involved in the suppressant effects of ibogaine and its analog, 18-MC, on alcohol intake and preference. It has been shown that ibogaine administration to rodents alters the levels of DA and its metabolites in the brain. Ibogaine induces prolonged (at least 19 h) decrease in the extracellular levels of DA metabolites in the nucleus accumbens, striatum and prefrontal cortex (Sloviter et al., 1980; Glick et al., 1993; Maisonneuve et al., 1991). Similar to ibogaine, systemic administration of 18-MC decreases extracellular levels of DA in the nucleus accumbens in rats suggesting that 18-MC may exert its suppressant effects on alcohol intake by the same mechanism as ibogaine. However, this compound has no apparent tremorigenic effect and even at a high dose (100 mg/kg) does not produce any neuronal toxicity (Glick et al., 1996). There is some evidence that ibogaine also interacts with serotonergic mechanisms in the brain believed to be involved in excessive alcohol intake. Ibogaine has been reported to increase 5-HT concentrations in rat nucleus accumbens (Broderick et al., 1992).

Another possible mechanism is the interaction of ibogaine and 18-MC with endogenous opioid system in the brain. Ibogaine congeners have been reported to have affinity for opioid receptors. It has been demonstrated that ibogaine interacts at the κ-opiate receptor (Deechar et al., 1992) and inhibits κ-mediated DA release in rats (Reid et al., 1994). There are several reports supporting the involvement of endogenous opioid system in the regulation of alcohol intake. Thus, it is possible that ibogaine and its analog exert their suppressant effects on alcohol intake by altering the endogenous opioid system. Other mechanisms have been suggested. These include the interaction of ibogaine with *N*-methyl-D-aspartate (NMDA) receptor-coupled cation channels (Popik et al., 1994) and with GABAergic systems, which have been implicated in alcohol-seeking behaviors. Although it appears that ibogaine and its analog exert their suppressant effect on alcohol intake by modulating several neuronal systems, the true mechanism of action of these compounds in attenuating alcohol intake is not fully understood. A firm conclusion awaits further pharmacological and behavioral studies.

5. General conclusions

With the current information, it can be concluded that several plant-derived compounds have been shown to significantly reduce alcohol intake in several animal models of excessive alcohol consumption. Although several neurotransmitter systems, including serotonergic, dopaminergic, GABAergic and opioidergic have been implicated in their attenuating effects on alcohol intake, the true mechanisms of action of these compounds are not fully understood. Until extensive careful clinical studies are carried out, it will be difficult to extrapolate the findings on animal models of alcoholism to a human population. Nevertheless, the extensive positive findings in animal models suggest that the outcome of clinical trials is likely to be positive as well especially when pharmacological treatment is combined with counseling.

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