

REVIEW

Phytotherapeutic approach to alcohol dependence: New old way?

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Abstract

Alcohol abuse and dependence represent a worldwide problem from both medical and social points of view. In Italy it is estimated that there are about one million alcohol-dependent subjects. The pharmacological treatment of patients with alcohol dependence plays a key role in order to achieve alcohol abstinence and prevent relapse. At present, the possible utility of the complementary medicines in the treatment of alcohol dependence is controversial. In the last years, pre-clinical and clinical data from traditional medicines suggest that novel pharmacological approaches for treatment of alcoholism and alcohol abuse may stem from natural substances. The present review summarizes the findings of the effects of phytotherapy in alcohol addiction.

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Keywords: Alcohol dependence; Addiction; Complementary medicine; Phytotherapy

Introduction

Alcohol is foreign to the human system and is normally destroyed in the liver by oxidation, yielding acetaldehyde, which is in turn destroyed by aldehyde dehydrogenase. Alcohol abuse and dependence hold an important role in the public health because of both the medical consequences and economical costs. In Italy it is estimated that there are approximately one million alcohol-dependent subjects and that in the year 2000 almost 100,000 patients were discharged from the public hospitals with a clinical diagnosis completely attributable to alcohol (Abenavoli et al. 2008). These data correspond to an overall rate of 172.2/100.000 persons. Alcohol abuse and the related consequences (i.e.,

alcohol-attributable mortality, productivity loss, absenteeism, hospitalization, etc.) have important implications in the social costs. In fact, alcohol abuse is estimated to be responsible for around 5–6% of the Italian Gross Domestic Product (Abenavoli et al. 2008).

The pharmacological treatment of patients with alcohol dependence plays a key role in achieving alcohol abstinence and prevent relapse, especially if it is conceived together with the psychosocial interventions already used for many years (Addolorato et al. 2005a, b). Within pharmacological approaches, some recent small preliminary data suggest the possible utility of the complementary medicines (CMs) in the treatment of alcohol dependence. CM is defined as “diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine” (Abenavoli et al. 2008). In spite of the utility of the CM being described in different diseases, the data concerning

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Table 1. Herbal drugs and herbal preparations traditionally used to help alcoholism.

Common name	Latin name	Part(s) of plant used	Key constituents
St. John's wort	<i>Hypericum perforatum</i>	Leaves and flowering tops	Phloroglucinol derivatives (hyperforin, adhyperforin), anthraquinone derivatives (hypericin, pseudohypericin)
Kudzu	<i>Pueraria lobata</i>	Flowers and roots	Isoflavons derivatives (daidzin, daidzein)
Danshen	<i>Salvia miltiorrhiza</i>	Roots	Diterpene compounds (tanshinones, miltirone)
Tabernanthe	<i>Tabernanthe iboga</i>	Roots	Ibogaine
Ginseng	<i>Panax ginseng</i>	Roots	Ginsenosides
Evening primrose	<i>Oenothera biennis</i>	Oil	GLA (an omega 6 fatty acid)
Milk Thistle	<i>Silybum marianum</i>	Fruits	Silymarin, a complex of 5 flavanolignans
Scullcap	<i>Scutellaria laterifolia</i>	Aerial parts	Flavonoids (scutellarin, scutellarein), iridoids (catalpol)
SKV ^a			
Agaricus ^b			

^aAn ayurvedic formula of 12 herbal ingredients. It is used to help alcoholism and other addictions.

^bA homeopathic product. It is recommended in cases of acute alcoholism and is a potent antidote against the ravages of a hangover.

its possible use in alcohol-dependent patients are controversial (Ernst 1996) and do not permit the drafting of final conclusions.

For several centuries, in particular in China, medicinal plants have been used for the treatment of alcohol dependence (Table 1). Recent lines of experimental evidence suggest that novel pharmacological approaches for the treatment of alcohol dependence could stem from some natural substances (Overstreet et al. 2003; Rezvani et al. 2003).

A recent study by our group (Bardazzi et al. 2006) highlighted that 16.50% of Italian Alcohol and Drug Addiction Services use CMs for alcohol dependence treatment, and in these services 10.08% of the patients are treated by phytotherapy. This review will discuss the effect of some vegetable drugs on alcohol dependence and their possible benefit.

Methodology

The keywords used for the literature search for this review were alcohol dependence, addiction, complementary medicine, phytotherapy, etc. The search was carried out using PubMed updated to March 2008. The references were chosen on the basis of their relevance to the text.

Hypericum perforatum L. (Fam Clusiaceae)

The antidepressant properties of the St. John wort – *Hypericum perforatum* L. (HPE) – have been well known

since the time of Hippocrates. Recent pre-clinical and clinical studies (Nahrstedt and Butterweck 1997) have demonstrated that HPE is effective in the treatment of mild to moderate therapy of anxiety.

HPE contains several biologically active compounds, including naphthodianthrones (hypericin and pseudohypericin), fluoroglucynol derivatives (hyperforin, adhyperforin), several flavonol glycosides, biflavones, phenylpropanes, proanthocyanidins, tannins, xanthenes and some amino acids such as gamma-aminobutyric acid (GABA) (Barnes et al. 2001). Several experimental and clinical studies identified hyperforin (Fig. 1A) as the major active principle for antidepressant action. Hyperforin is known to inhibit the uptake of aminergic transmitters such as serotonin and noradrenaline into synaptic nerve endings (Kumar et al. 2006). It also increases the extracellular levels of other transmitters including acetylcholine, glutamate, and GABA. These effects may be secondary to an increase of the intracellular sodium concentration mediated by openings of non-selective cation channels in the synaptosomal membrane (Treiber et al. 2005). Hyperforin also interacts with a variety of receptors and ion channels including glutamatergic and calcium channels (Chatterjee et al. 2001; Fisunov et al. 2000). However, the inhibitory effects of HPE on ethanol intake are not mediated by GABA agonist actions (Perfumi et al. 2002).

According to the high comorbidity between depressive states and alcohol dependence, some studies have investigated HPE efficacy in the alcohol-seeking behavior (Uzbay 2008). All of them were performed on experimental animals. It has been suggested that HPE

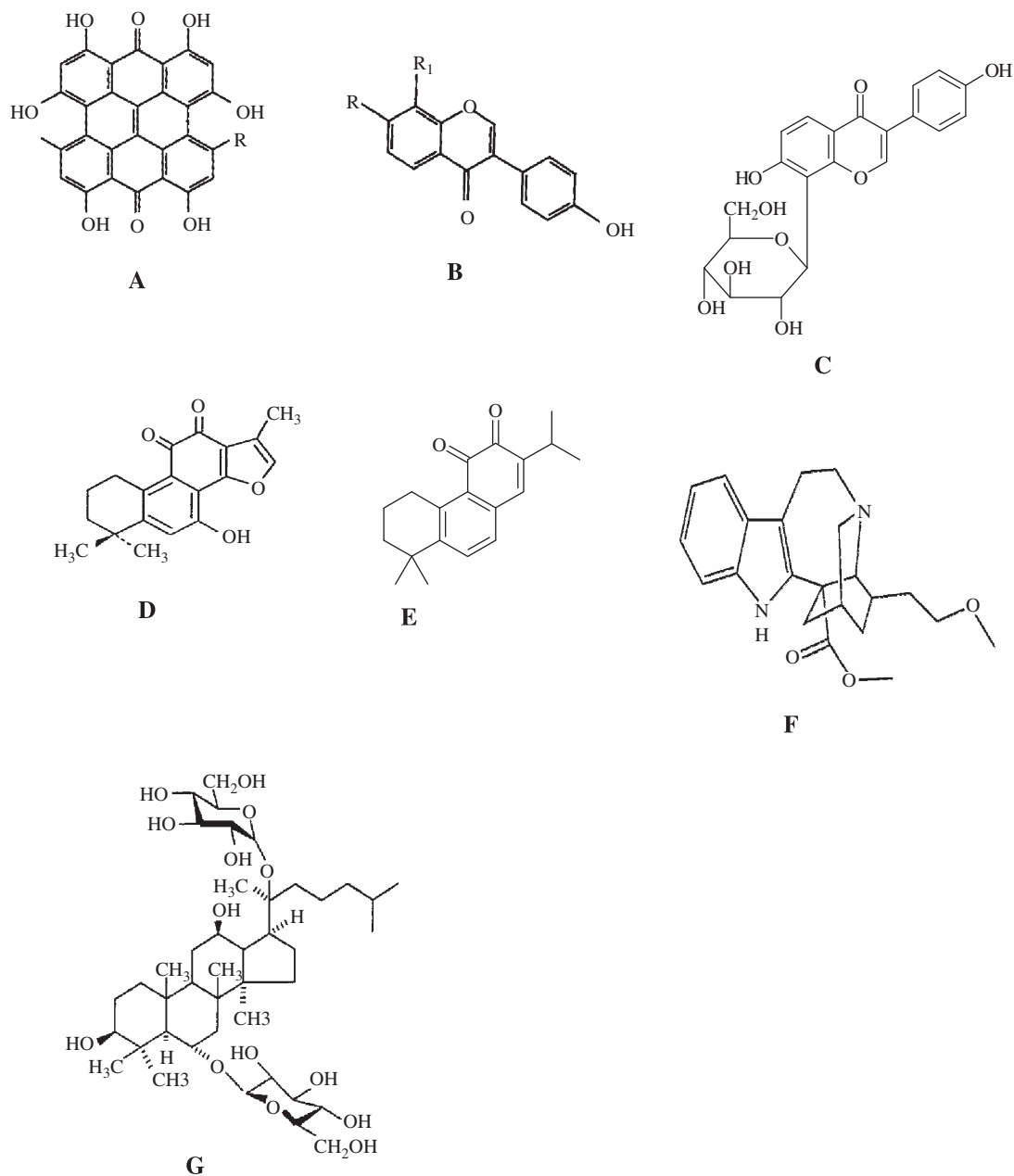


Fig. 1. Chemical formulas of hypoforin (A), daidzin (B), puerarin (C), tanshinone IIA (D), miltirone (E), 18-methoxycoronaridine (F), and a general structure of the ginsenosides (G).

inhibits ethanol intake and preference in several strains of ethanol-preferring rats and mice. The effect of HPE extract seems to be interrelated with the content of hyperforin. A recent report (Perfumi et al. 2005a) showed that HPE extract markedly and selectively reduced ethanol self-administration in the motivation for ethanol as revealed in the self-administration paradigm, as well as in the increased craving for ethanol observed after a period of ethanol deprivation. HPE extract was administered by means of an intra-gastric catheter, 1 h before the tests. For the self-administration experiments, the rats were trained to self-administer

10% ethanol in 30 min daily sessions under a fixed ratio 1 schedule of reinforcement. HPE extract was also tested on 0.2% saccharin self-administration. For the ethanol deprivation experiments, rats that had a previous experience with voluntary ethanol drinking were deprived of ethanol for 9 days, whereas water and food were freely available; HPE extract was given by intra-gastric injection 1 h before the ethanol re-presentation. HPE extract in doses of 31 or 125 mg/kg but not 7 mg/kg significantly reduced ethanol self-administration, while it did not modify saccharin self-administration. The same doses of the extract abolished the increased

ethanol intake following ethanol deprivation. These results, together with those obtained in voluntary drinking rats, strengthen the idea that the use of HPE may represent an interesting pharmacological approach to treat excessive alcohol drinking and prevent alcohol relapse in human alcoholics.

Opioid receptor antagonists, such as naloxone and naltrexone (NTX), have shown their efficacy to reduce alcohol intake, in both rats and humans, by lowering its rewarding and reinforcing properties (Overstreet et al. 1999; Perfumi et al., 2003). A pre-clinical study has evaluated the effect of chronic (once a day for 12 days) intra-gastric administration of an HPE extract, given alone or in combination with NTX, on ethanol intake offered 2 h/day in alcohol-preferring rats (Perfumi et al. 2005b). Chronic intra-peritoneal treatment with NTX reduced ethanol intake at 3 mg/kg, but not at 0.5 mg/kg. The synergistic effect on ethanol intake of HPE extract and NTX was evident also in conditions of chronic treatment. HPE extract, 7 mg/kg, and NTX, 0.5 mg/kg, evoked a pronounced and statistically significant reduction of ethanol intake, while being inactive. The effect of the combined treatment on ethanol intake remained stable over the 12 days of treatment; food intake was slightly reduced only on days 3 and 7 in response to 125 mg/kg of HPE extract combined with NTX 0.5 mg/kg, but no difference in body weight between controls and treated rats was observed at the end of treatment. Following a 12-day treatment with 125 mg/kg of HPE extract, no difference was observed in the responsivity of preferring rats to the effect on ethanol intake of several doses of the extract. This result suggests that the reduction of the motivational properties of alcohol by HPE and opioid receptor antagonists represents a converging mechanism that can explain the synergism of action of the two classes of compounds.

***Pueraria lobata* Owhi (Fam. Fabaceae)**

The anti-drunkenness properties of the extracts of *Pueraria lobata* (PL), also known as kudzu, have been known since the traditional Chinese medicine. An experimental study demonstrated that the daily intra-peritoneal administration of a crude extract of PL (1.5 g kg⁻¹ day⁻¹) roots halved alcohol intake in alcohol-preferring Syrian Golden hamsters, when a choice between alcohol solution and water was given (Keung and Vallee 1993). In this study, two putative active principles were identified. Indeed, the administration of the two major isoflavones present in PL extracts (daidzin and daidzein) reduced ethanol intake in Syrian Golden hamsters with an efficacy similar to the one observed using the PL extract. The ability of PL to reduce alcohol consumption in animals has been also showed testing a herbal mixture (intra-peritoneal injection

of 0.5, 0.75, and 1.0 g/kg; and oral administration of 1.5 g/kg), comprising PL (Overstreet et al. 1996). Interestingly, this mixture is commonly used in China to prepare the so-called “tea of sobriety”. Daidzin (Fig. 1B) is also a potent and selective inhibitor of human mitochondrial aldehyde dehydrogenase (ALDH-2). Some authors showed a direct correlation between ALDH-2 inhibition and ethanol intake suppression and increase the possibility that daidzin may suppress the ethanol intake of golden hamsters, by inhibiting ALDH-2 (Keung 2003).

Puerarin (Fig. 1C) represents the most concentrated isoflavonoid in kudzu, although it is not as potent as daidzin. The beneficial effects of puerarin on alcohol intake in alcohol-preferring rats reported in the literature also suggest the potential utility of puerarin as an anti-craving agent (Overstreet et al. 2003; Rezvani et al. 2003). According to the animal data, a preliminary clinical study explored the effect of kudzu root extract on 38 patients affected by alcohol dependence and were randomly assigned to receive either kudzu root extract (1.2 g twice daily) or placebo (Shebek and Rindone 2000). Sobriety level and a visual analogic scale to assess alcohol craving were assessed. Kudzu root appeared to be no better than placebo in reducing alcohol craving and/or promoting sobriety. Unfortunately the authors did not report the concentrations of the active isoflavones in their kudzu extract. More recently a study has tested the efficacy of a kudzu extract in a group of “heavy” alcohol drinkers, treated with either placebo or a kudzu extract (500 mg three times daily for 7 days) (Lukas et al. 2005). After the 7-day period, subjects had the opportunity to drink their preferred brand of beer in a naturalistic laboratory setting. Kudzu treatment resulted in significant reduction in the number of beers consumed, an increase in the number of sips and the time to consume each beer and a decrease in the volume of each sip. These changes occurred in the absence of a significant effect on the urge to drink alcohol. The authors concluded that kudzu may be a useful adjunct in reducing alcohol intake, although the exact mechanism by which kudzu suppresses ethanol intake remains to be clarified.

***Salvia miltiorrhiza* Bge. (Fam. Lamiaceae)**

The dried roots of *Salvia miltiorrhiza* (SM) are used in traditional Chinese medicine for the treatment of several pathologies (e.g., insomnia). Pre-clinical data suggest that extracts from the SM: tanshinone IIA, cryptotanshinone and miltirone (Figs. 1D, E) are effective in reducing voluntary alcohol intake in animal models of excessive alcohol drinking (Carai et al. 2000). Specifically, extracts of SM have been found to (a) delay the acquisition of alcohol-drinking behavior in

alcohol-naive rats given alcohol under the home-cage 2-bottle “alcohol versus water” choice regimen (Brunetti et al. 2003); (b) reduce voluntary alcohol intake under the two-bottle choice regimen in rats that were alcohol experienced at the time of extract administration; and (c) suppress the temporary increase in voluntary alcohol intake occurring after a period of deprivation from alcohol (Serra et al. 2003).

Recently the same study group (Colombo et al. 2006) has found that miltirone is the possible active chemical component responsible for the reducing effect of SM extracts on alcohol intake in Sardinian alcohol-preferring rats. The authors have assessed the effect of 100 mg/kg (intra-gastric administration) of four extracts of SM, differing in miltirone content (0%, 2%, 3%, and 7%), on alcohol intake in alcohol-experienced rats exposed to the two-bottle “alcohol (10%, volume in volume) versus water” choice regimen. Subsequently, the effect of pure miltirone (2.5–10 mg/kg, intra-gastric, i.e., a dose range comparable to its content in the effective doses of the active extracts) on acquisition and maintenance of alcohol-drinking behavior was evaluated in alcohol-naive and alcohol-experienced sP rats exposed to the two-bottle choice regimen. The effect of miltirone (10 mg/kg, intra-gastric) on blood alcohol levels was assessed after the intra-gastric and intra-peritoneal administration of alcohol. Finally, the effect of miltirone (30–100 mg/kg, intra-gastric) on the severity of alcohol withdrawal syndrome was evaluated in Wistar rats made physically dependent on alcohol by the repeated administration of intoxicating doses of alcohol. The authors reported that the reducing effect of four different extracts of SM on alcohol intake was positively and significantly correlated with their miltirone content. Pure miltirone reduced alcohol intake in alcohol-experienced rats and delayed acquisition of alcohol-drinking behavior in alcohol-naive rats. Similar to SM extracts, miltirone markedly reduced blood alcohol levels when alcohol was administered intra-gastric but not intra-peritoneal, suggesting that miltirone hampered alcohol absorption from the gastrointestinal system. Finally, miltirone failed to affect the severity of alcohol withdrawal syndrome in alcohol-dependent rats. The ability of miltirone to reduce alcohol intake in rats could be explained by the anxiolytic effect previously reported in the literature (Lee et al. 1991). Future studies are needed to clarify this mechanism.

***Tabernanthe iboga* H. Bn. (Fam. Apocynaceae)**

Ibogaine is a naturally occurring, psychoactive indole alkaloid derived from the roots of the rain forest shrub *Tabernanthe iboga* (TI). Indigenous peoples of Western Africa use ibogaine in low doses to combat fatigue, hunger, and thirst, and in higher doses as a sacrament in

religious rituals. The stimulating effects of TI have been well known for centuries. Ibogaine has been claimed to be effective in treating multiple forms of drug abuse, including morphine, cocaine, heroin, and nicotine (Overstreet et al. 2003; Rezvani et al. 2003). However, it has been proposed that ibogaine exerts its anti-craving effects by stimulating dopaminergic and serotonergic systems (Glick et al. 1991). Accordingly, TI seems to be able to markedly reduce voluntary alcohol intake in alcohol-preferring rats (Rezvani et al. 2003). This effect was not related to a possible interaction between TI and alcohol, as shown by the virtually equal blood alcohol levels in both ibogaine- and placebo-treated rats. It is also of interest that the reducing effect on alcohol intake has been observed only when ibogaine was injected intra-peritoneally or intra-gastrically but not when it was injected subcutaneously. Intra-peritoneal administration of 10, 30, and 60 mg/kg ibogaine induced 8%, 13%, and 25% reduction, respectively, in alcohol preference in rats (Rezvani et al. 1995). This feature suggests that the active principle of ibogaine could be a metabolite produced by the liver. 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-Methoxycoronaridine (18-MC) (Fig. 1F) appears to be such an analog. In animal models, 18-MC reduced intravenous morphine, cocaine, methamphetamine, and nicotine self-administration, oral alcohol and nicotine intake, and attenuated signs of opioid withdrawal, but had no effect on responding for a non-drug reinforcer and produced no apparent toxicity in comparison to ibogaine (Maisonneuve and Glick 2003). Another study (Rezvani et al. 1997) showed that a single injection (intra-peritoneal) of 5, 20, or 40 mg/kg 18-MC significantly reduced alcohol intake and preference in a dose-dependent manner in preferring rats.

It has been hypothesized that ibogaine and its analog exert their suppressant effect on alcohol intake by modulating several neuronal ways, in particular dopaminergic and serotonergic 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 (Overstreet et al. 2003; Rezvani et al. 2003).

***Panax ginseng* hayer (Fam. Araliaceae)**

There are some accounts of the effects of ginseng Meyer and its derivatives on alcohol intoxication. Early works recorded that ginseng saponines (Fig. 1G) increased the rate of oxidation of ethanol in alcohol-fed rats (Joo et al. 1982) and red ginseng extract prevented memory failure and excitation in alcohol-intoxicated

mice (Saito et al. 1984). Later, using healthy human volunteers Lee et al. (1987) demonstrated that in 10 out of 14 cases ginseng extract accelerated alcohol clearance by 31–51%. Ginseng saponines apparently stimulate the microsomal ethanol-oxidising system and the aldehyde dehydrogenase (ADH) enzyme action and therefore there is a faster removal of acetaldehyde with rapid shunting of excess hydrogen into lipid biosynthesis (Kwak and Joo 1988). It has been also shown that rats plasma levels are lower (–20%) when alcohol is administered orally with red ginseng extract than when alcohol is given alone. However, further studies (Lee et al. 1993) support the idea that ginseng may promote faster disposal and elimination of alcohol from blood after drinking. Obviously further studies are needed concerning the value of ginseng in the treatment of alcoholism and associated problems, e.g., memory loss and nervous reactions.

Conclusions

Alcohol abuse and alcoholism represent a worldwide problem, both from a medical and from a social point of view. In the past, the therapy for patients affected by alcoholism was based mainly on the psychological approach. In recent years the use of pharmacotherapy together with psychosocial interventions has enhanced the percentage of success in maintaining alcoholic patients in remission (Abenavoli et al. 2008). Medical interventions in the field of alcoholism are primarily aimed at relieving the consequences of alcohol withdrawal syndrome and arresting alcohol drinking, maintaining sobriety for as long as possible (Addolorato et al. 2005a, b). Pharmacotherapy is conceived to provide a substantial contribution to these goals, facilitating the psychological support and social rehabilitation of alcoholic patients (Addolorato et al. 2007). Recent experimental evidence and critical re-examination of empirical data from traditional medicines suggest that novel pharmacological approaches for treatment of alcoholism and alcohol abuse may stem from natural substances. Several plant-derived compounds have been shown to significantly reduce alcohol intake, mostly in animal studies. Although several neurotransmitter systems seem to be involved in their effects on alcohol-seeking behavior, the exact mechanisms of action of these compounds remain to be clarified. Until extensive clinical studies are carried out, it will be difficult to extrapolate the findings on animal models of alcohol dependence to a human cohort. The role of these compounds in the treatment of alcoholism will ultimately depend on the outcome of carefully conducted clinical trials. 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 psychological support counselling. Phytotherapy can be a new old way to treat alcohol addiction.

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