



## Pharmacology and toxicology of absinthe

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### Summary

Absinthe is a flavoured distilled liquor, emerald green in colour, turning to cloudy, opalescent white when mixed with water. It has inspired many prominent artists, writers and poets – Vincent Van Gogh, Oscar Wilde, Pablo Picasso and Ernest Hemingway just to name a few. Absinthe was first produced commercially in 1797 by Henry-Louis Pernod, who purchased the formula from a French exile living in Switzerland. The wormwood, *Artemisia absinthium*, is the chief flavouring ingredient of absinthe and the presence of monoterpene thujone in this drug was the reason for the prohibition of the production and sale of absinthe in many countries. Thujone is a toxic chemical present in wormwood and is responsible for the pharmacological and toxicological properties of absinthe.

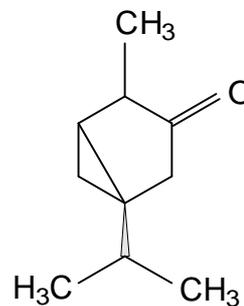
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### INTRODUCTION

Absinthe is bright green-colored alcoholic beverage, distilled from a variety of herbs extracted into an ethanol base. The drink was very popular in the 19<sup>th</sup> and early 20<sup>th</sup> centuries especially in France, but it was prohibited due to its toxicity. It was commonly imbibed by many artists and writers including Vincent van Gogh, Henri de Toulouse-Lautrec, Charles Baudelaire, and others, often inducing fits and hallucinations and sometimes contributing to psychoses and suicides (Vogt and Montagne, 1982, Arnold, 1988, 1989, 1992). Absinthe became an epidemic health problem and was banned in many countries early in the 20<sup>th</sup> century, but its use continues legally or illicitly even now (Strang et al. 1999, Holstege et al. 2002, Gambelunghe and Melai, 2002).

Thujone, one of the ingredients in the liquor, has been shown to cause brain damage, and is believed to be the compound responsible for the 1915 ban of the once highly popular drink. Absinthe has many supporters, yet most people have never heard of this extraordinary alcoholic beverage. It is illegal to make or sell absinthe in

many countries through out the world (Spain, Portugal, and the Czech Republic being exceptions); it is also illegal to own or use a still for the purpose without a license in many countries.



**I, alpha-thujone**

## ABSINTHE HISTORY

Wormwood is a venerable plant described in such historic texts as the Egyptian Ebers Papyrus (circa 3550 B.C) and the Bible. Extracts of wormwood were used to control gastrointestinal worms with records going back to ancient Egyptian times (Arnold 1989).

Wormwood and essential absinth oil as a flavouring agent and the source for preparation of some beverages has been used for centuries. For example its addition to wine was documented by the ancient Greeks during the reign of Pliny the Elder in 100 A.D. (Arnold 1989). Wormwood and absinthe are inseparably linked with European cultural history. Excessive consumption of wormwood products- absinthism- is connected with the neurotoxic effect of this drug, whose common name is derived from its former medicinal use to purge intestinal roundworms (Morrant 1993).

Absinthe manufacture is a complicated technological process initiated by steeping dried herbs, including some common wormwood (*Artemisia absinthium*), in ethyl alcohol and then distilling the steep liquor. The distillation is essential as wormwood contains extraordinarily bitter compounds called absinthins which must be excluded from the distillate. Fortunately absinthins are alcohol insoluble, while the rest of the essential oil is volatile with alcohol vapor. The product is then treated with Roman wormwood (*A. pontica*) and other herbs in a delicate and difficult final step.

## ABSINTHE DRINKING

The traditional method of drinking involves charging a perforated "absinthe spoon" with a sugar cube and placing it over an "absinthe glass" which greatly resembles a modern parfait ice cream glass. The glass has usually a line around it marking the proper amount of absinthe it should contain so that when full, the glass will hold the proper 5 parts of water for 1 part absinthe – almost no one ever drinks this liqueur neat, save for a few show-offs. The water is trickled over the sugar cube which slowly dissolves. As the sugary water dilutes the alcohol, the herbal oils in the high proof alcohol solution come out of solution, being almost insoluble in water. This liberates the hugely floral bouquet and produces a milky off-white drink. The clouding effect has a very strong aesthetic appeal to absintheurs.

There's just one problem. Absinthe has been illegal in America and most European countries since the early-1900s. Nowadays absinthe is

becoming known owing to the Internet. It is now making a comeback. In any case, these beverages produced in modern times in Czech Republic, Portugal, and Spain have very small amounts of thujone. Old absinthe contained about 260 ppm of alpha-thujone, present-day absinthe generally has less than 10 ppm of this compound. This means that unless it is used excessively or chronically, modern absinthe is fairly safe for human consumption. However, the US FDA does not share this view. It is true that wormwood oil with a high content of thujone is available from a home computer. People are able to obtain, via the Internet, a recipe for making the banned liqueur absinthe. Therefore some doctors in USA warn about such medical products available over the Internet. They think that thujone is unsafe for human consumption, but not so much that they ban all foods containing thujone. People there are not warned that the consumption of absinthe may cause hallucinations, tremors, convulsions, and paralysis over the long term (Patočka and Plucar, 2003).

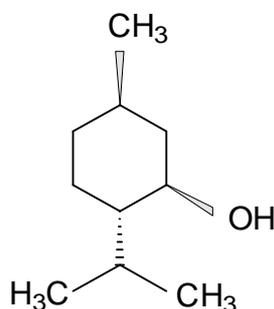
## CHEMICAL COMPOSITION

The chemical composition of absinth is very comprehensive and is determined by the chemical composition of the essential oil (up to 1.7%). It contains phellandrene, pinene, thujone (3 to 12%), thujyl alcohol and its esters (acetate, isovalerate, and palmitane), bisabolene, camphene, cadinene, nerol, and several azulenes: chamazulene, 3,6-dihydrochamazulene, and 5,6-dihydrochamazulene. The herb also contains bitter glucosides absinthin, absinthic acid, anabsinthin, aabsin, artametin, succinic acid together with tannin, resin, starch, malates, and some salts (Duke 1985).

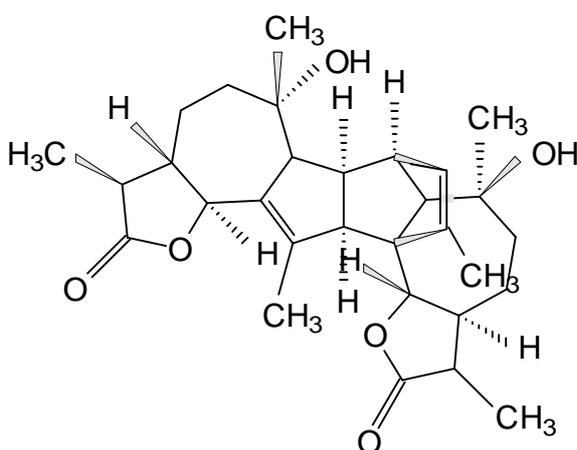
Thujone is probably the most important biologically active compound of absinthe. The sources of thujone in absinthe are the herbs wormwood (*A. absinthium*) and Roman wormwood (*A. pontica*). Thujone is named after the plant from which it was first extracted, thuja (*Thuja occidentalis*). Since thujone was also extracted from other plants before its structure was identified, it is also known as absinthol, tanacetone, and salviol.

The principal pharmacologically active compound of absinthe is monoterpene derived from the essential wormwood oil, known as thujone (I). Monoterpenes make a class of natural products containing ten carbons, found in many different plants and flowers. They are derived from the coupling of two isoprenoid units, which are made from isopentylpyrophosphate, a precursor in the

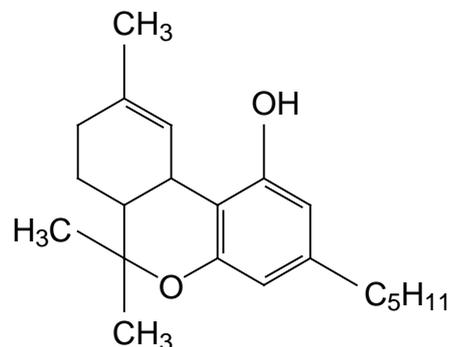
biosynthesis of cholesterol. These compounds are usually fragrance oils or low melting solids and are used commercially as aroma or flavoring agents. Thujone is structurally related to menthol (**II**), which is an old natural remedy for various complaints. Menthol contains a cyclohexane, or 6-membered, ring in its structure as well as an exocyclic isopropyl group. Thujone also contains a cyclohexane ring as well as the exocyclic isopropyl group. The essential difference is the presence of an additional 3-membered ring in thujone. This new ring results from an additional carbon-carbon bond between two of the members of the cyclohexane ring. Thujone is a chiral compound and only one of its stereoisomers, alpha-thujone, (+)-thujone, CAS 546-80-5, is present in this natural source and is also present in absinthe. Also present in the plant and in absinthe are strong bitter agents known as absinthin (**III**) and anabsinthin. These stimulate the digestive functions, including the gall bladder function (Simon et al. 1984).



**II, menthol**



**III, Absinthin**



**IV, Tetrahydrocannabinol (THC)**

#### PHARMACOLOGY

The psychological effects of absinthe were believed to be different from other alcoholic beverages. The liquor was believed to enhance the activity of the brain, develop new ideas, expand imagination, and act as an aphrodisiac. Therefore, the drink became very popular, especially with artists and writers such as de Maupassant, Toulouse Lautrec, Degas, Gauguin, Manet, and Oscar Wilde. Perhaps the most notable drinker was the troubled painter Vincent Van Gogh. During the last two years of his life, Van Gogh experienced fits of hallucinations and convulsions before his eventual suicide. His condition appears to have been worsened by his addiction to absinthe. Absinthe drinkers were reported to have experienced double action intoxication. This intoxication combined the separate effects of alcohol and thujone. While the alcohol produced a sedative effect in absinthe drinkers, thujone is reported to have caused excitation including visual and auditory excitation.

There is good evidence that both thujone and wormwood have psychoactive properties.

Thujone's mechanism of action is unknown. Some have suggested that the effect is due to thujone binding at the cannabinoid receptor, at which the active components in marijuana act (del Castillo et al. 1975). The neurotoxicity of thujone is believed to result from its structural similarity to tetrahydrocannabinol (THC) (**IV**), the active compound in marijuana. Thujone and THC have similar shapes, and it is believed that they interact with the same biological receptor to produce their similar psychological effects. Modeling studies show a good degree of overlap of thujone with THC. The hypothesis that alpha-thujone activates the CB1 cannabinoid receptor, based on the structural similarity of thujone enol to

tetrahydrocannabinol (del Castillo et al. 1975), was not supported experimentally.

It was found that the toxin alpha-thujone blocks brain receptors for gamma-aminobutyric acid (GABA). Without access to GABA, a natural inhibitor of nerve impulses, neurons fire too easily and their signaling goes out of control. Alpha-thujone also is reported to have antinociceptive activity in mice (Rice and Wilson, 1976). Meschler and Howett (1999) recently presented evidence that neither thujone, wormwood, nor HPLC fractions from oil of wormwood bind to the cannabinoid receptor at physiologically relevant concentrations. This finding confirms earlier but less direct evidence that thujone does not act at the cannabinoid receptor (Greenberg et al. 1978, Browne and Weissman, 1981, Rice and Wilson, 1976). It would seem that thujone acts through some other, yet unidentified, mechanism.

There have been several reports that wormwood has psychoactive effects. For example J. Ott in his book, *Pharmacothoeon*, writes that he tried smoking dried wormwood leaves and found it had a definite psychoactive effect (Ott 1993). Pendell (1994) repeated this experiment with similar effects. Furthermore, various other species of the *Artemisia* genus have been smoked and used as intoxicants in other cultures. *Artemisia nilagirica* is reportedly smoked in West Bengal for its psychoactive effects (Pal and Jain 1989). Similarly, *Artemisia caruthii* is inhaled by the Zuni as an analgesic (Ott 1993). However, these experiments yield little insight into the active component(s) of wormwood and whether these components play a role in absinthe's effects. For example, despite being smoked for its psychoactive effects, an assay of *Artemisia nilagirica* oil found it contained less than one percent total thujones (<http://216.239.37.100/search?q=cache:-wxBddUuYIUC:chemweb.calpoly.edu/chem/bailey/377/PapersSp2000/Ann/absinthe.html+artemisia+nilagirica+%2B+thujone&hl=cs&ie=UTF-8>).

There are also indications that thujone itself is psychoactive. Rice and Wilson (1976) have found that alpha-thujone, the dominant isomer in wormwood oil, has an antinociceptive (pain killing) effect, comparable to codeine, when injected subcutaneously in rats. Because the effect is stereospecific and not elicited by similar compounds, the researchers suggest that alpha-thujone acts at a specific but still unknown pharmacological site.

Also some other absinthe components can be biologically active. For example absinthine is listed as a narcotic analgesic in the same group as codeine and dextromethorpan.

The green color of absinthe is caused by oil of wormwood, anise (*Pimpinella anisum*), elecampane

(*Inula helenium*), majoram (*Origanum majorana*), and several other herbs. This mixture has an aphrodisiacal effect on both sexes, and acts much like a narcotic.

## TOXICOLOGY

Alpha-thujone is the principal active ingredient of wormwood oil and toxic principle in absinthe (Arnold 1988). It is also the active ingredient of wormwood oil and some other herbal medicines and is reported to have antinociceptive, insecticidal, and anthelmintic activity. The content of beta-thujone often exceeds that of alpha-thujone depending on the plant source, but the beta-diastereomer is generally of lower toxicity. The plant *Artemisia absinthium* and wormwood oil have insecticidal properties (Grainge and Ahmed, 1988), and alpha-thujone was one of the two most toxic monoterpenoids tested against western corn rootworm larvae (Lee et al. 1997). Public mistrust of synthetic pharmaceuticals and pesticides has led to the increasing popularity of herbal medicines and botanical insecticides even though they have not been subjected to the same rigorous tests of safety and evaluation of toxicological mechanisms (Coats 1994, Matthews et al. 1999). The toxic effects of alpha-thujone in mammals are well established but the mode of neurotoxic action is not fully known (Bonkovsky et al. 1992). Alpha-thujone is neurotoxic in rats (Millet et al. 1981). Furthermore, it is not even clear that thujone is present in sufficient quantities to play a role in the absinthe intoxication of humans. If cca 1.5 oz of absinthe is consumed (diluted with water) per drink (Vogt & Montagne 1982), it is equivalent to 2-4 mg of thujone. This is far below the level at which acute pharmacological effects are observed. Even chronic administration of 10 mg/kg oral thujone to rats does not alter spontaneous activity or conditioned behavior (Pinto-Scognamiglio 1968). Max (1990) is of the opinion that the literature on the pharmacology of thujone is too often extrapolated far beyond the experimental base. However, it is possible that thujone accumulates in the body and plays a role in the psychoactivity and toxicity of chronic absinthe use.

The i.p. LD<sub>50</sub> of alpha-thujone in mice is about 45 mg/kg and the toxicity curve is very sheer. With a dose of 30 mg/kg no death was observed and with a dose of 60 mg/kg 100 % mortality was recorded. Mice at the higher dose undergo a tonic convulsion leading to death within 1 min whereas at 30-45 mg/kg they exhibit tail-raising within the first 2 min, followed by flexion of the trunk and clonic activity of the forelimbs, progressing to generalized

and protracted tonic/clonic convulsions that ultimately result in death or recovery. The only proven effect of thujone, however, is its toxicity to the brain. Thujone may play a role in absinthe, but the evidence is not conclusive. Finally, it should be noted that by focusing on one component of wormwood oil, we ignore the many other poorly characterized compounds in wormwood and absinthe's other herbal ingredients which may play some role in absinthe's intoxicating and toxic effects.

Intraperitoneal administration of diazepam or phenobarbital 15 min before alpha-thujone at 100 mg/kg results in almost all of the mice surviving this otherwise lethal dose. Ethanol i.p. pretreatment at 1 g/kg also protects against the lethal effects of alpha-thujone at 100 mg/kg whereas a lower dose (0.5 g/kg) was ineffective. In experiments with *Drosophila* LC<sub>50</sub> 12 mg/tube was estimated whereas on the Rdl-strain resistant to dieldrin LC<sub>50</sub> 65 mg/tube was obtained. This finding showed that *Drosophila* of the dieldrin-resistant (*Rdl*) strain are also resistant to alpha-thujone.

Alpha-thujone modulates the GABA<sub>A</sub> receptor based on four observations. Comparison with picrotoxinin, the classical GABA<sub>A</sub> receptor antagonist, revealed similar poisoning signs and in both cases alleviation of toxicity by diazepam, phenobarbital, and ethanol (Kulkarni et al. 1990, Enna et al. 1997). Most importantly, electrophysiological studies establish that in dorsal root ganglion neurons alpha-thujone is a reversible modulator of the GABA<sub>A</sub> receptor. Alpha-thujone is a competitive inhibitor of ethynylbicycloorthobenzoate (EBOB) binding, i.e., of the noncompetitive blocker site of the GABA-gated chloride channel (Ratra et al. 2001).

Absinthe and wormwood oil contain not only alpha-thujone as their purported active ingredient but also many other candidate toxicants, including beta-thujone and ethanol in the case of absinthe, but alpha-thujone is the most common candidate on the neurotoxicity principle. Beta-thujone is less toxic than alpha-thujone to mice (Rice and Wilson, 1976) and *Drosophila* and in addition is 2.3-fold less potent in the [<sup>3</sup>H]EBOB assay. Current low levels of alpha- and beta-thujone in absinthe are of much less toxicological concern than the ethanol content (Strang et al. 1999). Another possibility exists that the toxic effect of thujone is realized by means of its metabolites. Alpha-thujone as other monoterpenes is easily metabolized.

The single report on metabolism identifies thujol and neothujol probably as conjugates in the urine of thujone-treated rabbits (Ishida et al. 1989). Höld et al. (2001) found enzymatic reduction of alpha-thujone to thujol and neothujol in low yield by rabbit but not mouse liver cytosol with NADPH.

The mouse liver microsomal P450 system rapidly converts alpha-thujone to 7-hydroxy-alpha-thujone as the major metabolite and the diastereomers of 4-hydroxythujone and some other hydroxythujones as minor metabolites. The various hydroxythujones probably are not the terminal metabolites because they are expected to undergo conjugation and excretion. However, the presence of hydroxythujones in the brain suggests their potential importance in the neurotoxicity. From this point of view there are two principal candidate toxicants: alpha-thujone and its 7-hydroxy metabolite. The 7-hydroxy compound was found in the brain at much higher levels than the parent alpha-thujone, suggesting possible conversion *in situ*, but this oxidation was not observed on incubation of alpha-thujone with brain microsomes and NADPH. Alpha-thujone compared with 7-hydroxy-alpha-thujone is 56-fold more potent in the [<sup>3</sup>H]EBOB binding assay and much more toxic to mice and houseflies. It appears that all of the metabolites are detoxification products, i.e., less toxic than alpha-thujone. Importantly, alpha-thujone appears at much lower levels and is less persistent than 7-hydroxy-alpha-thujone. At severely toxic alpha-thujone doses (40–60 mg/kg) the levels in the brain at 30 min after administration of alpha-thujone were 0.3–1.0 ppm for alpha-thujone and 1.5–8.4 ppm for 7-hydroxy-alpha-thujone with much higher levels (11 and 29 ppm for alpha-thujone and 7-hydroxy-alpha-thujone, respectively) at 2.5 min when the poisoning signs are most intense. The minor hydroxythujone metabolites are detectable only up to 20 min after the 50 mg/kg alpha-thujone dose. The discovery of alpha-thujone and its metabolite in brain suggests that either one or both may contribute to the toxic manifestations. Unfortunately, the metabolism of alpha-thujone in humans is not known.

## CLINICAL COURSE

Absinthe drinking caused both acute and chronic toxicity. The acute effect of absinthe came on rapidly after ingestion and evoked a cheerful mood, euphoria, a sharpened sense of perception, a sense of well being, followed by visual hallucinations, restlessness, giddiness, vomiting, vertigo, muscular disturbances and convulsions. Also angry excitement, impulsive violence and paranoia were very often observed. Serious absinthe poisoning is characterized by coma, respiratory arrest and death. Chronic effects of absinthe drinking include lack of appetite, gastritis, repeated vomiting, progressive mental deterioration and disorder, psychosis,

enormous visions, terrible dreams, nightmares, forgetfulness and painful reminiscence, weakening of the intellect, seizures, tremors and coma. Absinthe drinking is addictive and causes personality changes because of cortical damage which can lead to recurrent and sporadic seizures resembling epilepsy. Also the interruption of absinthe drinking is linked with serious clinical manifestations. The delirium associated with abstinence from absinthe was said to be more severe than that of ethanol breakdown. Because many of the effects of chronic absinthism are presumably irreversible, only supportive care is indicated. Seizures should be treated by standard anticonvulsive therapeutics such as benzodiazepines. Psychosis should be managed with neuroleptic medication.

## CONCLUSIONS

Absinthe is a bright green liquor flavored using an herbal extract, very popular in the 19<sup>th</sup> century especially in France within the bohemian crowd. Chronic use of absinthe leads to absinthism. The symptoms for this addiction include epileptic attacks, hallucinations, and delirium. Due to this and other social considerations, absinthe was banned in many countries during the early part of the 20<sup>th</sup> century. Nowadays absinthe is making a comeback.

This alcoholic beverage is coming to be known owing to the Internet and is picking up new users. It can be perilous because few people know about absinthe neurotoxicity .

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