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α-Thujone (the active component of absinthe): γ-Aminobutyric acid type A receptor modulation and metabolic detoxification

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ABSTRACT

Other Sections▼

α-Thujone is the toxic agent in absinthe, a liqueur popular in the 19th and early 20th centuries that has adverse health effects. It is also the active ingredient of wormwood oil and some other herbal medicines and is reported to have antinociceptive, insecticidal, and anthelmintic activity. This study elucidates the mechanism of α-thujone neurotoxicity and identifies its major metabolites and their role in the poisoning process. Four observations establish that α-thujone is a modulator of the γ-aminobutyric acid (GABA) type A receptor. First, the poisoning signs (and their alleviation by diazepam and phenobarbital) in mice are similar to those of the classical antagonist picrotoxinin. Second, a strain of *Drosophila* specifically resistant to chloride channel blockers is also tolerant to α-thujone. Third, α-thujone is a competitive inhibitor of [^{3}H]ethynylbicycloorthobenzoate binding to mouse brain membranes. Most definitively, GABA-induced peak currents in rat dorsal root ganglion neurons are suppressed by α-thujone with complete reversal after washout. α-Thujone is quickly metabolized *in vitro* by mouse liver microsomes with NADPH (cytochrome P450) forming 7-hydroxy-α-thujone as the major product plus five minor ones (4-hydroxy-α-thujone, 4-hydroxy-β-thujone, two other hydroxythujones, and 7,8-dehydro-α-thujone), several of which also are detected in the brain of mice treated i.p. with α-thujone. The major 7-hydroxy metabolite attains much higher brain levels than α-thujone but is less toxic to mice and *Drosophila* and less potent in the binding assay. The other metabolites assayed are also detoxification products. Thus, α-thujone in absinthe and herbal medicines is a rapid-acting and readily detoxified modulator of the GABA-gated chloride channel.

Other Sections▼

Absinthe was a popular emerald-green liqueur in the 19th and early 20th centuries. It was commonly imbibed by artists and writers including Vincent van Gogh, Henri de Toulouse-Lautrec, and Charles Baudelaire, often inducing fits and hallucinations and sometimes contributing to psychoses and suicides (1–5). Absinthe became an epidemic health problem and was banned in many countries early in the 20th century, but its use continues legally or illicitly even now (6, 7). The toxic properties of absinthe are attributable to wormwood oil used in making the beverage. Wormwood oil is in itself a prevalent herbal medicine for treating loss of appetite, dyspeptic disorders, and liver and gallbladder complaints (8, 9).

α-Thujone (Fig. 1) generally is considered to be the principal active ingredient of wormwood oil and toxic principle in absinthe (2). The content of β-thujone often exceeds that of α-thujone depending on the plant source, but the β-diastereomer (Fig. 1) is generally of lower toxicity. α-Thujone also is reported to have antinociceptive activity in mice (10). This monoterpenoid occurs in many plants, including *Artemesia* species, sage, and the Thuja tree (4). Extracts of wormwood were used to control gastrointestinal worms with records back to ancient Egyptian times (4). *Artemesia absinthium* and wormwood oil have insecticidal properties (11), and α-thujone was one of the two most toxic monoterpenoids tested against western corn rootworm larvae (12). 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 (13–15).

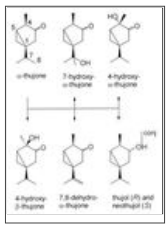


Figure 1

Structures of α-thujone (1*S*, 4*R*, 5*R*-thujone) and its metabolites in the mouse liver microsomal P450 system, the brain of treated mice, and the urine of treated rabbits. The hydroxythujones and dehydro-α-thujone are observed in the mouse liver microsomal P450 system and in brain whereas thujol and neothujol are identified in the rabbit liver cytosolic ketone reductase system and in urine as conjugates. The major metabolite in mouse brain and the P450 system is 7-hydroxy-α-thujone. β-Thujone is the 1*S*, 4*S*, 5*R* diastereomer (structure not shown).

The toxic effects of α-thujone in mammals are well established but the mode of neurotoxic action is poorly understood. It is porphyrogenic, possibly thereby contributing to the absinthe-induced illness of Vincent van Gogh (5, 16). α-Thujone is neurotoxic in rats (17), and ingestion of wormwood oil containing α-thujone recently resulted in human poisoning (18). The hypothesis that α-thujone activates the CB_1 cannabinoid receptor, based on the structural similarity of thujone enol with tetrahydrocannabinol (19), was not supported experimentally (20). The convulsant action led to multiple speculations on mechanisms, one of which was antagonism of the γ-aminobutyric acid (GABA) receptor system (20), a proposal that was not explored further. α- and β-Thujone are reduced in rabbits from the ketones to the corresponding alcohols (thujol and neothujol) (21) of unknown toxicity but no other metabolites are identified.

The goals of this study are to define the mechanism of neurotoxicity of α-thujone and identify its major metabolites (Fig. 1) and their role in the poisoning process. Emphasis is placed on the hypothesis that the convulsant action is caused by modulating the GABA-gated chloride channel.

MATERIALS AND METHODS

Other Sections▼

Chemicals.

Sources were: α-thujone (≈99% purity) from Fluka; wormwood oil (3.2% α- and 35% β-thujone) from Lhasa Karnak (Berkeley, CA) and absinthe with 0.4 ppm α-thujone, 5 ppm β-thujone, and 50% (vol/vol) ethanol labeled Herring Absenta (Zaragoza, Spain) with concentrations based on analyses in this laboratory; picrotoxinin, diazepam, and sodium phenobarbital from Sigma; dieldrin and α-endosulfan from Chem Service (West Chester, PA); [^{3}H]ethynylbicycloorthobenzoate ([^{3}H]EBOB) (38 Ci/mmol) from NEN. Although not detailed here, 7-hydroxy-α-thujone, 4-hydroxy-α-thujone, 4-hydroxy-β-thujone, 7,8-dehydro-α-thujone, and a thujol/neothujol mixture were synthesized as standards for comparison with metabolites.

Toxicity to Mice.

Male albino Swiss–Webster mice (22–28 g) were treated i.p. with the test compound by using propylene glycol (2 μl/g body weight) as the carrier vehicle. Prophylactic i.p. treatments also were examined for their effect on α-thujone toxicity (100 mg/kg) individually with ethanol (0.5 or 1.0 g/kg as 20% and 40% solutions in saline, 20 min pretreatment), diazepam (1 mg/kg, 15 min pretreatment), or phenobarbital (15 mg/kg, 15 min pretreatment).

Toxicity to *Drosophila*.

Fruit flies (*Drosophila melanogaster*) were used in two types of assays: comparing two strains known to be different in sensitivity to insecticidal chloride channel blockers and comparing α-thujone and its metabolites for toxicity to the susceptible strain. The median lethal concentration (LC_{50}) was determined for α-thujone and dieldrin with two strains of *Drosophila*: a dieldrin-resistant *Rdl*$^{MD\text{-}RR}$ strain (22, 23) (obtained from the Bloomington *Drosophila* Stock Center at Indiana University, Bloomington) and the *Canton-S*, wild-type sensitive (*S*) strain. The test chamber was a glass tube (12 × 75 mm) containing a filter paper strip (Whatman no. 1, 8 × 65 mm). Five adult flies were placed in the tube, which then was closed with a single layer of parafilm. A solution of α-thujone or dieldrin in propylene glycol (5 μl) was injected with a 10-μl syringe through the parafilm onto the filter paper after which the tube was covered with a second piece of parafilm. Mortality was recorded after 8 h at 25°C as flies that could not move. The experiment was repeated four times to prepare dosage mortality curves for calculation of resistance ratios (LC_{50} *Rdl*/LC_{50} *S*).

Effect on [^{3}H]EBOB Binding in Mouse Brain Membranes.

Mouse brain membranes were prepared and depleted of GABA as described (24). For inhibitor potency assays, the membranes (200 μg protein) were incubated with the test compound (added in DMSO, final concentration 1%) and [^{3}H]EBOB (0.7 nM) in 1.0 ml of 10 mM sodium phosphate, pH 7.5 buffer containing 200 mM sodium chloride at 37°C for 70 min (25). Scatchard analyses were performed with no inhibitor and with 5 and 25 μM α-thujone by using [^{3}H]EBOB at 0.08–26 nM. The inhibitory potency also was compared for ethanol and absinthe (based on ethanol content) with that for ethanol containing 5 μM α-thujone. The incubated mixtures were filtered through GF/C glass fiber filters, then rinsed twice with 5 ml of ice-cold 0.9% sodium chloride, by using a cell harvester. Specific binding was considered to be the difference between total binding and nonspecific binding determined in the presence of 5 μM α-endosulfan {a potent GABA type A ($GABA_A$) receptor antagonist and specific inhibitor of [^{3}H]EBOB binding}.

Effect on GABA-Induced Whole-Cell Currents.

Rat dorsal root ganglion neurons were prepared and cultured as described (26). Currents were induced by 10-msec pulses of 300 μM GABA and recorded by using the whole-cell patch clamp technique. The GABA-induced inward current of this preparation was carried by chloride ions through open chloride channels (27). Each cell was tested for the degree of suppression caused by bath application of α-thujone to determine the concentration for 50% inhibition (IC_{50}).

GC-MS Identification and Analysis of α-Thujone and Metabolites.

Standard analytical methods of GC-MS and derivatization of alcohol and ketone functionalities were applied to

α-thujone and its metabolites. Analyses used the DB-5 fused silica gel capillary column (30 m, 0.25 mm i.d., 0.25 μm film thickness) (J&W Scientific, Folsom, CA). The initial column temperature of 80°C was programmed to 200°C at the rate of 5°C/min, followed by an increase at 20°C/min to 300°C where it was maintained for 2 min. The carrier gas and reagent gas were helium and methane, respectively. Temperatures of the injection port and detector were 250°C and 280°C, respectively. The mass spectrometer was operated in the positive chemical ionization mode. One microliter was injected splitless onto the column. For quantitation, the GC-MS was operated in the selected ion monitoring (SIM) mode, measuring *m/z* 135 for α-thujone and *m/z* 151 for the hydroxythujones, dehydrothujone, and (*S*)-(−)-carvone (internal standard). The concentration of each analyte was determined from least-squares equations generated from peak-area ratios of α-thujone, 7-hydroxy-α-thujone, and the internal standard. Identification of α-thujone and metabolites involved comparison with standards by cochromatography and MS fragmentation patterns as parent compounds and two derivatives. Trimethylsilyl ethers were formed on reaction of alcohols with *N*-methyl-*N*-trimethylsilyltrifluoroacetamide and methyloximes on coupling ketones with methoxyamine. These derivatization procedures and MS fragmentation patterns also allowed assignment of some metabolites as hydroxythujones without specifying the position of hydroxylation.

Enzymatic Metabolism.
Rabbit or mouse liver cytosol (1 mg protein) or washed mouse liver microsomes (1 mg protein) and NADPH (or other cofactor, 1 mM final concentration) were incubated with α-thujone (30 μg, 0.2 μM final concentration) in 100 mM phosphate, pH 7.4 buffer (1 ml) for 1 h at 37°C. For analysis the internal standard *S*-carvone (0.05 μg) was added in ethanol (10 μl), and the mixture was saturated with sodium chloride and extracted with ethyl acetate (3 ml) for 30 min by gentle rocking. The organic extract, recovered by centrifugation at 900 *g*, was almost completely evaporated (but never to dryness) under a stream of nitrogen at room temperature and reconstituted in ethyl acetate (50 μl) for GC-MS analysis. Recovery values by this procedure for α-thujone and the major metabolite were >60% with no degradation during GC.

Analysis of Brain.
Mice were treated i.p. with α-thujone. At appropriate times thereafter the animals were killed and whole brains were removed for analysis. They were rinsed and homogenized in 10 ml of 100 mM phosphate, pH 7.4 buffer. The internal standard was added as above. The mixtures were centrifuged at 1,500 × *g* for 10 min. The pellet was resuspended in 2 ml of phosphate buffer, sonicated for 1 min, and centrifuged, and the supernatant fractions were combined. The samples were extracted with ethyl acetate (6 ml) and analyzed as described in *Enzymatic Metabolism*.

RESULTS

Other Sections▼

α-Thujone Is a Convulsant.
The i.p. LD_{50} of α-thujone in mice is about 45 mg/kg, generally with 0% and 100% mortality at 30 and 60 mg/kg, respectively. 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. Intraperitoneal administration of diazepam or phenobarbital 15 min before α-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 (but not at 0.5 g/kg) also protects against the lethal effects of α-thujone at 100 mg/kg.

α-Thujone Cross-Resistance in *Drosophila* Strain Resistant to Dieldrin.
Flies of the *Rdl* strain (>55-fold resistant to dieldrin; LC_{50} >275 μg/tube for *Rdl* versus 5 μg/tube for *S*) are 5-fold resistant to α-thujone (LC_{50} 65 μg/tube for *Rdl* versus 12 μg/tube for *S*) (Fig. 2). This finding establishes moderately high insecticidal activity for α-thujone and cross-resistance in the dieldrin-resistant strain.

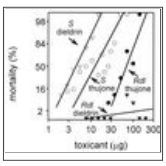


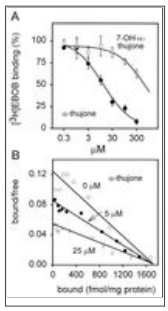
Figure 2

Drosophila of the dieldrin-resistant (*Rdl*) strain are also resistant to α-thujone. The susceptible (*S*) strain is *Canton S*. Concentration is shown on a logarithmic scale and mortality on a probit scale.

α-Thujone Inhibition of [^{3}H]EBOB Binding.
The IC_{50} of α-thujone for [^{3}H]EBOB binding in mouse brain membranes is 13 ± 4 μM (Fig. 3*A*). The binding of α-thujone is competitive with that of [^{3}H]EBOB based on Scatchard analysis (Fig. 3*B*). For comparison, other IC_{50} values are 29 ± 8 μM for β-thujone, 37 ± 8 μM for wormwood oil (calculated as molecular weight of thujone), and 0.6 ± 0.1 μM for picrotoxinin (inhibition curves not shown).

Figure 3

α-Thujone and 7-hydroxy-α-thujone inhibit [^{3}H]EBOB binding to mouse brain membranes. (*A*) IC_{50} determination for α-thujone and 7-hydroxy-α-thujone (mean ± SEM, n = 4). (*B*) Scatchard plots as average of duplicate measurements for [^{3}H]EBOB alone (K_d 2.8 nM and B_{max} 1,700 fmol/mg protein) and with α-thujone at 5 μM (K_d 4.1 and B_{max} 1,700) and 25 μM (K_d 7.2 and B_{max} 1,700).



α-Thujone Modulation of the $GABA_A$ Receptor-Chloride Channel.

The currents induced by 300 μM GABA are suppressed with 30 μM bath-applied α-thujone and there is full reversal on washing with α-thujone-free solution (Fig. 4 *A* and *B*). The IC_{50} for α-thujone is 21 μM in suppressing the GABA-induced currents (Fig. 4*C*).

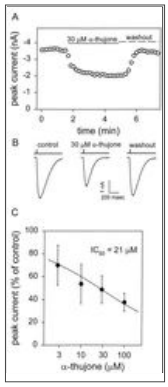


Figure 4

Suppression of GABA-induced peak currents by bath application of α-thujone. Currents were induced by 300 μM GABA (10 msec) pulses. The peak amplitude of current decreased with 30 μM α-thujone and recovered after washing with α-thujone-free solution. (*A*) Time course of 30 μM α-thujone-induced changes in peak current amplitude. (*B*) Representative current records. (*C*) Concentration-response relationship (mean ± SD, *n* = 4–5).

Absinthe, Ethanol, and Ethanol Containing α-Thujone as Inhibitors of [^{3}H]EBOB Binding.

The inhibitory effects on [^{3}H]EBOB binding were compared for absinthe, ethanol, and ethanol containing α-thujone to help understand their independent and combined actions on the chloride channel. The IC_{50} for absinthe (based on ethanol content) is 263 ± 47 mM and for ethanol is significantly higher at 370 ± 4 mM (Fig. 5 *A*). There is no significant interaction between the effects of ethanol and α-thujone (Fig. 5*B*), i.e., α-thujone (5 μM) inhibition is 20–30% independent of ethanol concentration up to 300 mM.

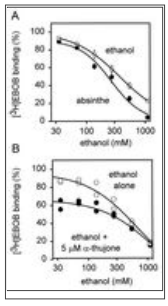


Figure 5

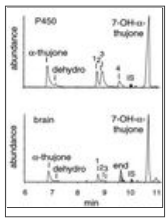
Absinthe, ethanol, and ethanol containing α-thujone inhibit [^{3}H]EBOB binding to mouse brain membranes. (*A*) Comparison of an absinthe preparation (based on ethanol content) with ethanol (average of duplicate measurements or mean ± SD, *n* = 6). (*B*) Comparison of ethanol with ethanol containing 5 μM α-thujone (average of duplicate measurements).

Metabolism of α-Thujone by Liver Enzymes.

Incubation of α-thujone with rabbit (but not mouse) liver cytosol gives thujol and neothujol, identified by GC-MS comparison with authentic standards *per se* and by forming trimethylsilyl (but not methyloxime) derivatives. This enzymatic reduction depends on NADPH but occurs in small yield. Metabolism in mouse liver microsomes is a much more facile reaction and gives no thujol or neothujol but instead different products. α-Thujone is stable on incubation with mouse liver microsomes alone but is almost completely metabolized when NADPH (but not NADP, NADH, or NAD) also is added. Six NADPH-dependent microsomal metabolites are evident by GC-MS, each at higher retention time than the parent α-thujone (Fig. 6). The first-eluting metabolite is identical in GC and MS features to synthetic 7,8-dehydro-α-thujone. The next five metabolites each are converted to trimethylsilyl and methyloxime derivatives, indicating the presence of both an alcohol substituent and a ketone functionality. Synthesis of various hydroxythujones and their comparison with the metabolites (directly, and as trimethylsilyl ethers and methyloximes) identifies the major product as 7-hydroxy-α-thujone and two minor metabolites as the diastereomers of 4-hydroxythujone.

Figure 6

Representative GC-MS- selected ion monitoring chromatograms for α-thujone and metabolites extracted from the mouse liver microsome-NADPH (P450) system and the brain of α-thujone-treated mice (50 mg/kg, i.p., 10 min after treatment). The major metabolite is 7-hydroxy-α-thujone. Four minor hydroxythujone metabolites are as follows: 1) 4-hydroxy-α; 3) 4-hydroxy-β; 2 and 4) others. Dehydro refers to 7,8-dehydro-α-thujone. Shaded peaks not derived from α-thujone are an endogenous substance (end) and the internal standard (IS). All thujone-derived metabolites fall within the chromatographic region shown.



Metabolites in the Brain of α-Thujone-Treated Mice.

The brain contains α-thujone, dehydro-α-thujone, and four hydroxythujones (7-hydroxy-α major plus 4-hydroxy-α, 4-hydroxy-β, and one other) also observed in the liver P450 system (Fig. 6). Identifications are based on retention times and MS fragmentation patterns both direct and as trimethylsilyl and methyloxime derivatives. The brain levels of α-thujone and 7-hydroxy-α-thujone are dose- and time-dependent after i.p. injection of α-thujone (Fig. 7). Importantly, α-thujone appears at much lower levels and is less persistent than 7-hydroxy-α-thujone. At severely toxic α-thujone doses (40–60 mg/kg) the levels in brain at 30 min are 0.3–1.0 ppm for α-thujone and 1.5–8.4 ppm for 7-hydroxy-α-thujone (Fig. 7*A*) with much higher levels (11 and 29 ppm for α-thujone and 7-hydroxy-α-thujone, respectively) at 2.5 min (Fig. 7*B*) when the poisoning signs are most intense. The minor hydroxythujone metabolites are detectable only up to 20 min after the 50 mg/kg α-thujone dose.

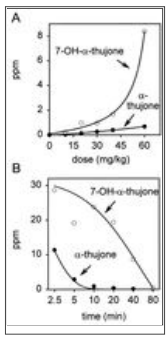


Figure 7

Brain levels of α-thujone and 7-hydroxy-α-thujone as a function of dose and time in mice treated i.p. with α-thujone. Average of determinations on two mice except for a single determination at 5 min. (*A*) Dose studies at 30 min after treatment. (*B*) Time studies at 50 mg/kg.

Biological Activities of Metabolites.

Synthetic standards of the metabolites shown in Fig. 1 except the 4-hydroxy-α-thujone diastereomers were compared with α-thujone for potency as toxicants to mice and *Drosophila* and inhibitors of [^{3}H]EBOB binding. The discriminating levels used were 50 mg/kg i.p. for mice and 50 μg/tube for the *S* strain of *Drosophila*. With mice, α-thujone is lethal, whereas 7-hydroxy-α-thujone, dehydro-α-thujone, and thujol/neothujol are not lethal. With *Drosophila*, α-thujone gives complete mortality, dehydro-α-thujone gives 70% mortality, and 7-hydroxy-α-thujone and thujol/neothujol give about 30% mortality. In the [^{3}H]EBOB binding assay, 7-hydroxy-α-thujone gives an IC_{50} value of 730 ± 265 μM versus 13 ± 4 μM for α-thujone (Fig. 3*A*), whereas the value for dehydro-α-thujone is 149 ± 10 μM (inhibition curve not shown).

DISCUSSION

Other Sections▼

This study establishes that α-thujone modulates the $GABA_A$ receptor based on four observations. Comparison with picrotoxinin, the classical $GABA_A$ receptor antagonist, revealed similar poisoning signs and in both cases alleviation of the toxicity by diazepam, phenobarbital, and ethanol (28, 29). *Drosophila* with a single point mutation in the *Rdl* GABA receptor subunit of Ala^{302} to Ser conferring resistance to dieldrin (22, 23) is also resistant to α-thujone, albeit to a lesser degree. α-Thujone is a competitive inhibitor of [^{3}H]EBOB binding, i.e., of the noncompetitive blocker site of the GABA-gated chloride channel (25). Most importantly, electrophysiological studies establish that in dorsal root ganglion neurons α-thujone is a reversible modulator of the $GABA_A$ receptor.

Absinthe and wormwood oil contain not only α-thujone as their purported active ingredient but also many other candidate toxicants, including β-thujone and ethanol in the case of absinthe. β-Thujone is less toxic than α-thujone to mice (10) and *Drosophila* and in addition is 2.3-fold less potent in the [^{3}H]EBOB assay (this investigation). Ethanol also enhances neuronal $GABA_A$ receptor function (30) and therefore might suppress the blocking action of α-thujone in absinthe. However, ethanol does not alter the inhibitory action of α-thujone on [^{3}H]EBOB binding. The α- and β-thujone content of the absinthe sample examined here (0.4 and 5 ppm or 2.6 and 33 μM, respectively) may be a contributing factor in the somewhat greater potency of absinthe (based on ethanol content) than of ethanol *per se* in the [^{3}H]EBOB assay. However, the 10 ppm (66 μM) upper limit of the European Commission (6) and particularly the 260 ppm (1710 μM) thujone content of old absinthe (6) would give a detectable to major inhibitory effect beyond that of the ethanol content. Current low levels of α- and β-thujone in absinthe are of much less toxicological concern than the ethanol content (6).

α-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 (21). We find enzymatic reduction (possibly by a cytosolic ketone reductase) (31) of α-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 α-thujone to 7-hydroxy-α-thujone (major), the diastereomers of 4-hydroxythujone (minor), and other hydroxythujones (minor). Interestingly, the major sites of P450 hydroxylation at the 4- and 7-positions are those involving

intermediate tertiary radicals that are more stable than secondary and primary radicals. Dehydro-α-thujone also is observed and may arise from dehydration of the 7-hydroxy compound as a biological reaction because this possible conversion is not an artifact during the extraction and analysis procedure. 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.

Metabolic detoxification is a dominant feature of α-thujone neurotoxicity in mice. There are two principal candidate toxicants, α-thujone and its 7-hydroxy metabolite. The 7-hydroxy compound is present in brain at much higher levels than the parent α-thujone, suggesting possible conversion *in situ*, but this oxidation was not observed on incubation of α-thujone with brain microsomes and NADPH. α-Thujone compared with 7-hydroxy-α-thujone is 56-fold more potent in the [^{3}H]EBOB binding assay and much more toxic to mice and houseflies. It appears that all of the metabolites studied here are detoxification products, i.e., less toxic than α-thujone. However, the level in brain of 7-hydroxy-α-thujone is several-fold greater than that of α-thujone (e.g., 29 and 11 ppm, respectively, at the time of severe poising signs), suggesting that either one or both may contribute to the toxic manifestations.

This study establishes that α-thujone acts at the noncompetitive blocker site of the $GABA_A$ receptor and is rapidly detoxified, thereby providing a reasonable explanation for some of the actions of absinthe other than those caused by ethanol, and allowing more meaningful evaluation of risks involved in the continued use of herbal medicines containing α-thujone.

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ABBREVIATIONS

EBOB	ethynylbicycloorthobenzoate or 4′-ethynyl-4-*n*-propylbicycloorthobenzoate
GABA	γ-aminobutyric acid
$GABA_A$ receptor	type A GABA receptor
LC_{50}	median lethal concentration

FOOTNOTES

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FIGURES AND TABLES

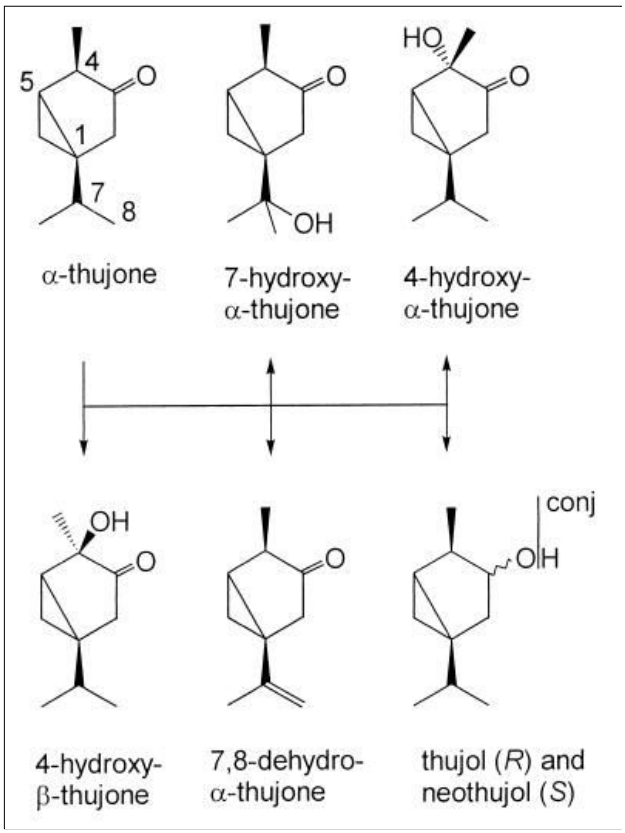

Figure 1

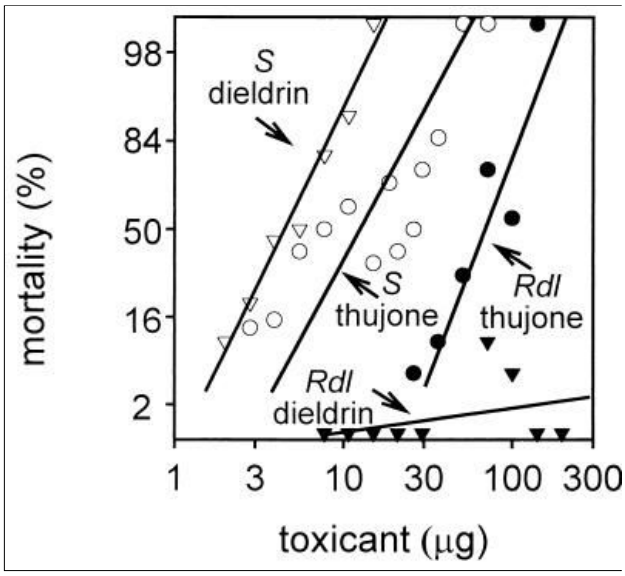
98
84
50
16
2
mortality (%)
S
dieldrin
S
thujone
Rdl
thujone
Rdl
dieldrin
1
3
10
30
100
300
toxicant (μg)

Figure 2

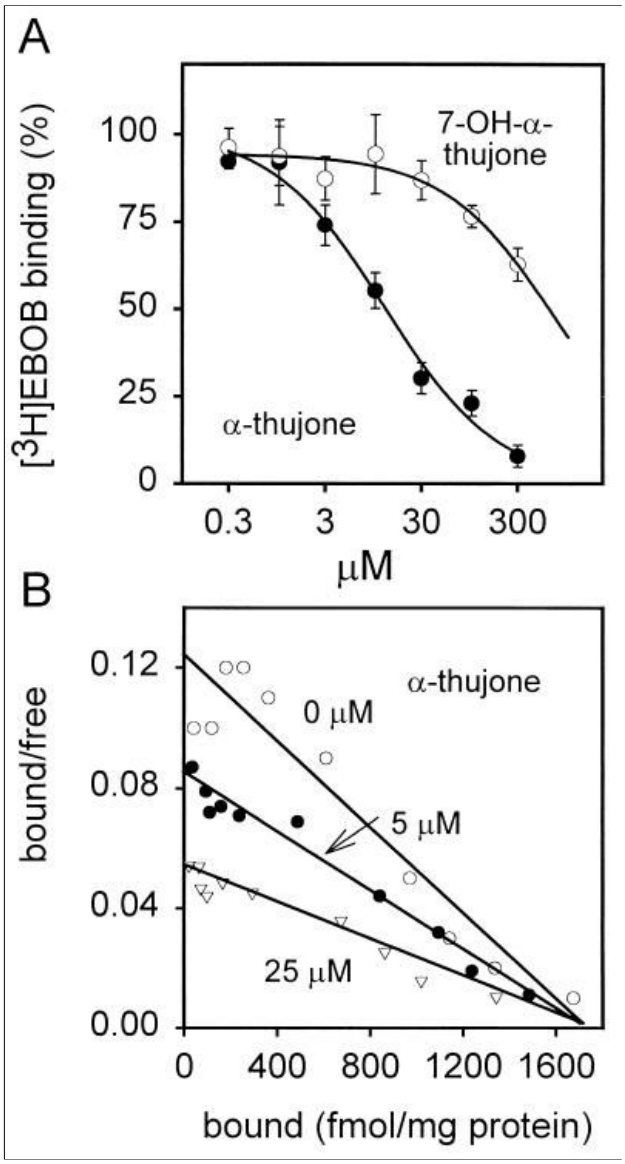
A
[3H]EBOB binding (%)
100
75
50
25
0
7-OH-α-thujone
α-thujone
0.3
3
30
300
μM
B
bound/free
0.12
0.08
0.04
0.00
α-thujone
0 μM
5 μM
25 μM
0
400
800
1200
1600
bound (fmol/mg protein)

Figure 3

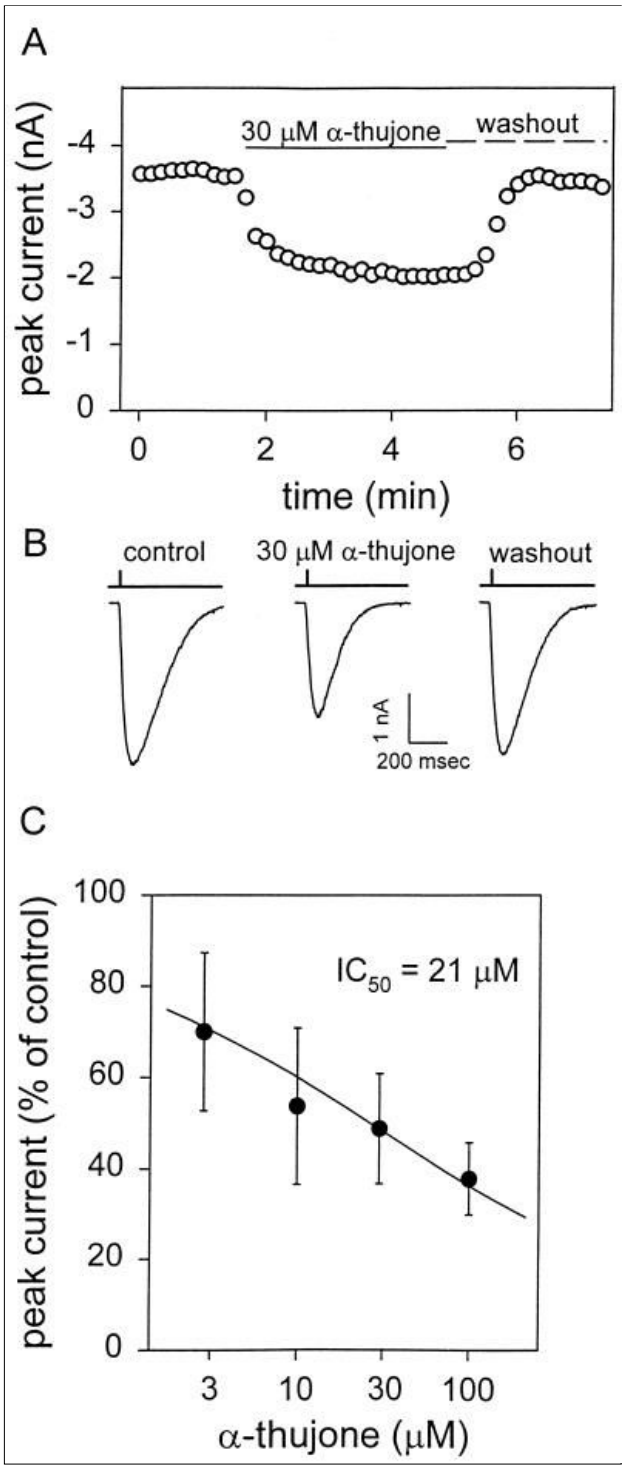
A
peak current (nA)
-4
-3
-2
-1
0
30 μM α-thujone
washout
0
2
4
6
time (min)
B
control
30 μM α-thujone
washout
1 nA
200 msec
C
peak current (% of control)
100
80
60
40
20
0
IC50 = 21 μM
3
10
30
100
α-thujone (μM)

Figure 4

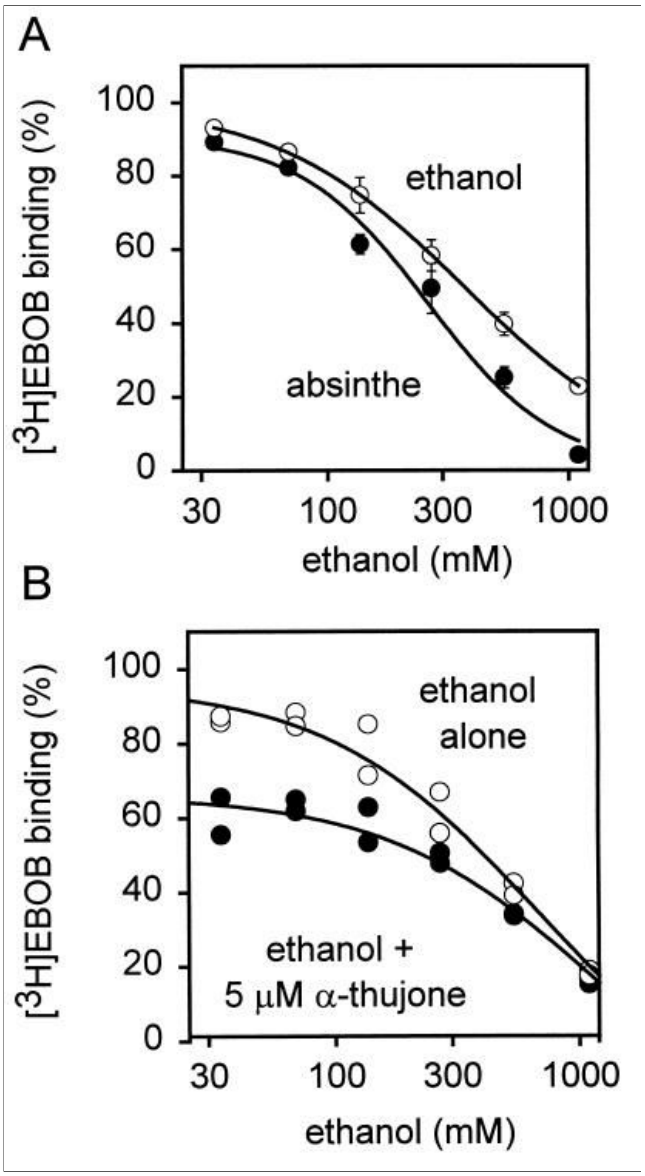
A
[3H]EBOB binding (%)
100
80
60
40
20
0
ethanol
absinthe
30
100
300
1000
ethanol (mM)
B
[3H]EBOB binding (%)
100
80
60
40
20
0
ethanol
alone
ethanol +
5 μM α-thujone
30
100
300
1000
ethanol (mM)

Figure 5

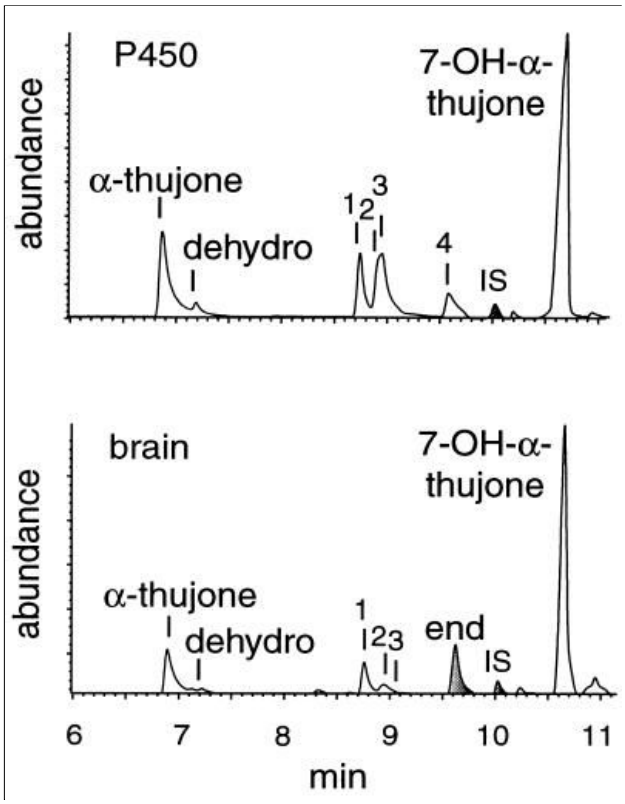
P450
7-OH-α-thujone
α-thujone
dehydro
1
2
3
4
IS
abundance
brain
7-OH-α-thujone
α-thujone
dehydro
1
2
3
end
IS
abundance
6
7
8
9
10
11
min

Figure 6

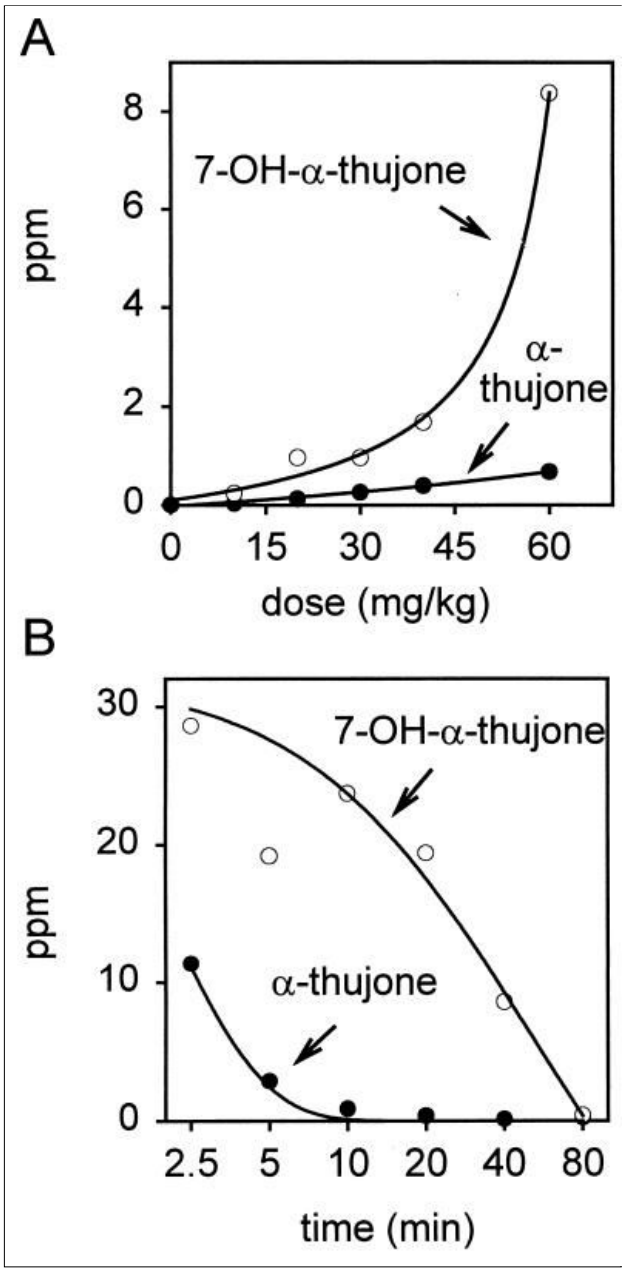

Figure 7

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Absinthe and gamma-aminobutyric acid receptors.
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Detection of errors of interpretation in experiments in enzyme kinetics.
(PMID:11384193)

The effects of neuroleptics on the GABA-induced Cl- current in rat dorsal root ganglion neurons: differences between some neuroleptics.
(PMID:11906969)

Acetoacetate, acetone, and dibenzylamine (a contaminant in l-(+)-beta-hydroxybutyrate) exhibit direct anticonvulsant actions in vivo.

(PMID:11952765)

Drug interactions at GABA(A) receptors.
(PMID:12126658)

Thirteen-week repeated dose toxicity study of wormwood (Artemisia absinthium) extract in rats.
(PMID:14746350)

Alpha-thujone reduces 5-HT3 receptor activity by an effect on the agonist-reduced desensitization.
(PMID:15002407)

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(PMID:15231641)

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(PMID:16599645)

Absinthism: a fictitious 19th century syndrome with present impact.
(PMID:16722551)

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(PMID:16891209)

Anticonvulsant mechanisms of the ketogenic diet.
(PMID:17241207)

Absinthe--is its history relevant for current public health?
(PMID:17982755)

The ketogenic diet in a pill: is this possible?
(PMID:19049610)

Effects of the essential oils of Lippia turbinata and Lippia polystachya (Verbenaceae) on the temporal pattern of locomotion of the mosquito Culex quinquefasciatus (Diptera: Culicidae) larvae.
(PMID:19085007)

Ketogenic diets: evidence for short- and long-term efficacy.
(PMID:19332337)

5-HT(3) receptors: role in disease and target of drugs.
(PMID:20621123)

Repellence of essential oils of aromatic plants growing in Argentina against Aedes aegypti (Diptera: Culicidae).
(PMID:20838809)

Thujone corrects cholesterol and triglyceride profiles in diabetic rat model.
(PMID:21740283)

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[1992]

Anisatin modulation of the gamma-aminobutyric acid receptor-channel in rat dorsal root ganglion neurons.
(PMID:10455311)
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[1980] - Academic (Orlando, FL)

Genes & Proteins

Found 1 unique Genes closely

related to this citation

Rdl: Resistant to dieldrin
(NCBI gene:39054)

Found 2 unique Proteins closely related to this citation

Gamma-aminobutyric acid receptor
(FlyBase:Q7JPT1)
Gamma-aminobutyric acid receptor subunit beta
(FlyBase:P25123)

Identified 4 unique Genes/Proteins in the Full Text

Rdl (1)
type A (1)
CB1 (1)
cytochrome P450 (1)

Gene Ontology (GO) Terms

Identified 7 unique GO Terms in the Full Text

binding (17)
microsomes (5)
membranes (5)
cytosol (3)
death (2)
excretion (1)
conjugation (1)

Species

Identified 14 unique Species in the Full Text

mice (29)
(mouse)
Drosophila (11)
rabbits (5)
flies (3)
rat (3)
houseflies (1)
animals (1)
Drosophila melanogaster (1)
Fruit flies (1)
human (1)
mammals (1)
western corn rootworm (1)
Thuja (1)
plants (1)

Diseases

Identified 5 unique Diseases in the Full Text

tonic/clonic convulsions (1)
convulsion (1)
suicides (1)
psychoses (1)
hallucinations (1)

Chemicals

Identified 32 unique Chemicals in the Full Text

Thujone (132)
ethanol (24)
GABA (14)
chloride (9)
dieldrin (8)
NADPH (7)
Trimethylsilyl (5)
ketones (5)
diazepam (5)
phenobarbital (4)
ethyl acetate (3)
sodium chloride (3)
antagonist (3)
ethers (2)
carvone (2)
glycol (2)
propylene (2)
endosulfan (2)
monoterpenoid (2)
monoterpenes (1)
NAD (1)
NADH (1)
NADP (1)
methyl (1)
methane (1)
helium (1)
silica (1)
sodium phosphate (1)
sodium phenobarbital (1)
enol (1)
botanical insecticides (1)
anthelmintic (1)

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