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Thujone—Cause of absinthism?

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Abstract

Habitual abuse of the wormwood spirit absinthe was described in the 19th and 20th centuries as a cause for the mental disorder ''absinthism'' including the symptoms hallucinations, sleeplessness and convulsions. A controversial discussion is going on if thujone, a characteristic component of the essential oil of the wormwood plant *Artemisia absinthium* L., is responsible for absinthism, or if it was merely caused by chronic alcohol intoxication or by other reasons such as food adulterations.

To ascertain if thujone may have caused absinthism, absinthes were produced according to historic recipes of the 19th century. Commercial wormwood herbs of two different manufacturers, as well as self-cultivated ones, were used in a concentration of 6 kg/100 l spirit. In addition, an authentic vintage Pernod absinthe from Tarragona (1930), and two absinthes from traditional small distilleries of the Swiss Val-de-Travers were evaluated. A GC–MS procedure was applied for the analysis of α- and β-thujone with cyclodecanone as internal standard. The method was shown to be sensitive with a LOD of 0.08 mg/l. The precision was between 1.6 and 2.3%, linearity was obtained from 0.1 to 40 mg/l ($r = 1.000$).

After the recent annulment of the absinthe prohibition all analysed products showed a thujone concentration below the maximum limit of 35 mg/l, including the absinthes produced according to historic recipes, which did not contain any detectable or only relatively low concentrations of thujone (mean: 1.3 ± 1.6 mg/l, range: 0–4.3 mg/l). Interestingly, the vintage absinthe also showed a relatively low thujone concentration of 1.8 mg/l. The Val-de-Travers absinthes contained 9.4 and 1.7 mg/l of thujone.

In conclusion, thujone concentrations as high as 260 mg/l, reported in the 19th century, cannot be confirmed by our study. With regard to their thujone concentrations, the hallucinogenic potential of vintage absinthes can be assessed being rather low because the historic products also comply with today's maximum limits derived to exclude such effects. It may be deduced that thujone plays none, or only a minor role in the clinical picture of absinthism.

Keywords: Thujone; Absinthe; Absinthism; *Artemisia absinthium* L.; GC–MS

1. Introduction

The spirit drink known as absinthe was created in French-speaking Switzerland in the late 18th century. The herb of wormwood (*Artemisia absinthium* L.), used as medicine since the antiquity, was mixed for the first time with further herbal ingredients for flavouring and after the addition of alcohol distilled and distributed as foodstuff. In the late 19th century, absinthe, in the meantime called ''green fairy'' (''fée verte''), was the most popular spirit drink in Europe. The green coloured drink was consumed by the population of all social levels. Especially in the bars and cafés of Paris, the ''green hour'' (''l'heure verte'') was a steady element of the daily routine [1].

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The chronic abuse in the zenith of absinthe in the 19th and 20th centuries was made responsible for a syndrome called ''absinthism'' and was described to cause the following symptoms: after consuming absinthe, at first the well-being had been stimulated, later hallucinations had arisen followed by a depressive phase. Prolonged drinking of absinthe had caused convulsions, blindness, hallucinations, and mental deterioration. In the advanced state, signs of degeneration could be observed, which could cause convulsions that even resulted in death [2–8].

However, only as a result of the mass consume in the beginning of the 20th century, absinthe was blamed for all kinds of diseases and its prohibition was demanded. In 1905, absinthe was prohibited in Belgium, followed by Switzerland in 1908, The Netherlands in 1910, the USA in 1912 and Italy in 1913 [5,9]. In France, absinthe was prohibited in 1915, because of the misuse in the French military during the First World War [7,9]. Finally in 1923, absinthe was also prohibited in Germany [10].

According to the Council Directive 88/388/EEC on the approximation of the laws of the Member States relating to flavourings for use in foodstuffs and source materials for their production, the addition of thujone (Fig. 1) containing plants (such as wormwood) was re-allowed in the European Union [11]. After the obligatory adoption of the Directive by the member states in the early 1990s, absinthe was marketable again within the whole European Union. For bitter spirit drinks, such as absinthe, a thujone maximum limit of 35 mg/kg α-/β-thujone was introduced in the Directive. Over 10 years after the annulment of the prohibition, more than a hundred absinthe types are currently sold, which are mainly distributed as en-vogue drinks via the Internet. In bars, absinthe is served as a cocktail or long drink [12]. Recently, the absinthe prohibition was removed from the Swiss constitution, so that even more high-grade absinthe products produced according to traditional Swiss recipes are expected on the market in the future [13].

Despite the adopted maximum limits, the renaissance of absinthe led to fears of the return of absinthism [7,8,14] and its cause is discussed controversially. In most instances, the bicyclic monoterpene thujone as the main component of wormwood oil was blamed for absinthism because the thujone content of historic absinthe was speculated to be as high as 260 mg/l [15,16]. In contrast according to the opinion of Strang et al. [17], absinthism can be traced back to chronic alcohol intoxication alone causing similar symptoms. Pollmer [18] describes the adulteration of absinthe with toxic plants, such as sweet calamus (*Acorus calamus* L.) or tansy (*Tanacetum vulgare* L.), or adulteration with antimony chloride and copper sulphate as a possible cause of absinthism. Especially copper, whose re-sorption is amplified in combination with massive alcohol ingestion, may cause alcoholic cirrhosis in alcoholics [18]. Also, the use of inferior alcohol should be kept in mind as a possibility, because it explains symptoms such as impaired vision.

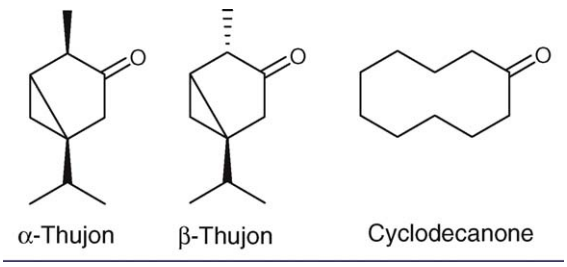

Fig. 1. Structures of α-thujone, β-thujone and the internal standard cyclodecanone.

In this work, the influence of thujone as cause for absinthism is investigated by analysing current and vintage products, as well as absinthes produced according to historic recipes.

2. Experimental

2.1. Reagents and materials

Chemicals (α-thujone, α-/β-thujone–isomere mixture, cyclodecanone) were purchased by Fluka (Buchs, Switzerland). Wormwood (*Artemisia absinthium* L., Asteraceae) was obtained from Caesar & Loretz (Hilden, Germany) and Bombastus–Werke (Freital, Germany).

2.2. Production of historic absinthes

Historic absinthes were prepared after recipes of Bedel [19]. The following three recipes were chosen, because they required the highest wormwood content: ''Swiss Absinthe of Pontarlier'', ''White Swiss Absinthe'', and ''Absinthe of Neufchatel''. Details of the recipes are available in Table 1. The whole process was done on a laboratory scale using a 1 l distillation still.

2.3. Influence of storage

The influence of storage on the thujone content of a commercial absinthe and a self-produced ''Swiss Absinthe of Pontarlier'' was determined using defined conditions. The absinthes were exposed to ultraviolet (UV) light for 5–25 h using a 360 W high-pressure mercury lamp Psorilux 3060 (Heraeus, Hanau, Germany) with UV-A doses of 16.9 mW/cm^2 and UV-B doses of 3.9 mW/cm^2. The thermal stability was evaluated by heat treatment at 50 °C for 5–25 h. In addition, five absinthes were stored at ambient temperatures in dark for 1 year.

2.4. Sample preparation

The sample preparation was done using liquid–liquid-extraction with 1,1,2-trichloro-1,2,2-trifluoroethane after a method of Rapp et al. [20]. After addition of 350 μl of

Table 1
Recipes of historic absinthes after Bedel [19]

	Swiss Absinthe of Pontarlier	White Swiss Absinthe	Absinthe of Neufchatel
Preparation	2.5 kg of wormwood, other herbs and 95 l of alcohol (85 vol%)	4 kg of wormwood, other herbs and 95 l of alcohol (85 vol%)	6 kg of wormwood, other herbs and 15 l of alcohol (85 vol%)
Maceration (h)	12	12	24
Distillation	Add 45 l of water and distill slowly to obtain 95 l	Add 45 l of water and distill slowly to obtain 95 l	Add 15 l water and distill to obtain 15 l
Colouration	Colour distillate with 1 kg of wormwood and other herbs at 50 °C	(No colouration)	Artificial food dyes
Adjustment to drinking strength	Adjust to 74 vol% (approximately 100 l)	Add water to obtain 100 l	Add to this product 65 l alcohol (85 vol%) and 20 l of water

cyclodecanone as internal standard (freshly prepared methanolic solution, 20 μg/ml), 2 ml of sample were shaken with 10 ml of ethanol (15%, v/v) and 1 ml of 1,1,2-trichloro-1,2,2-trifluoroethane for 60 s, and centrifuged at 3000 rpm for 5 min for phase separation. The lower organic phase was drawn off using a transferpettor and filled in a GC vial. For calibration, thujone solutions (0.1–40 mg/l) were freshly prepared in ethanol (15%, v/v) and extracted as the samples. The organic extracts were stored at 4 °C until analysis. No significant loss of analytes was detected by storage of up to 4 weeks.

2.5. GC–MS method

The GC–MS system used for analysis was an Agilent model 6890 Series Plus gas chromatograph in combination with a CTC Combi PAL autosampler and an Agilent 5973N mass selective detector. Data acquisition and analysis were performed using standard software supplied by the manufacturer. Substances were separated on a fused silica capillary column (HP-Innowax, 60 m × 0.25 mm i.d., film thickness 0.25 μm). Temperature program: 45 °C hold for 1 min, 5 °C/min up to 180 °C, 25 °C/min up to 240 °C, hold for 5 min. The temperatures for the injection port, ion source, quadrupole and interface were set at 220, 230, 150 and 250 °C, respectively. Split/splitless injection mode (1 μl, split ratio 5:1) and helium with a flow rate of 1.0 ml/min as carrier gas was used.

To determine the retention times and characteristic mass fragments, electron impact (EI) mass spectra of the analytes were recorded by total ion monitoring. The two diastereomers α-thujone (1*S*, 4*R*, 5*R*-thujone) and β-thujone (1*S*, 4*S*, 5*R*-thujone) as well as the internal standard cyclodecanone were baseline separated. The retention times were 17.2 min for α-thujone, 17.7 min for β-thujone and 25.1 min for cyclodecanone. For quantitative analysis, the chosen diagnostic mass fragments were monitored in the selected ion-monitoring (SIM) mode. α-/β-Thujone: *m/z* 110 as target ion and *m/z* 81 and 152 as qualifier ions; cyclodecanone: *m/z* 111 as target ion and *m/z* 98 and 154 as qualifier ions. For quantification, peak area ratios of the analytes to the internal standard were calculated as a function of the concentration of the substances.

2.6. Validation studies

For the validation of the method, authentic absinthe samples were prepared and analysed using the procedure

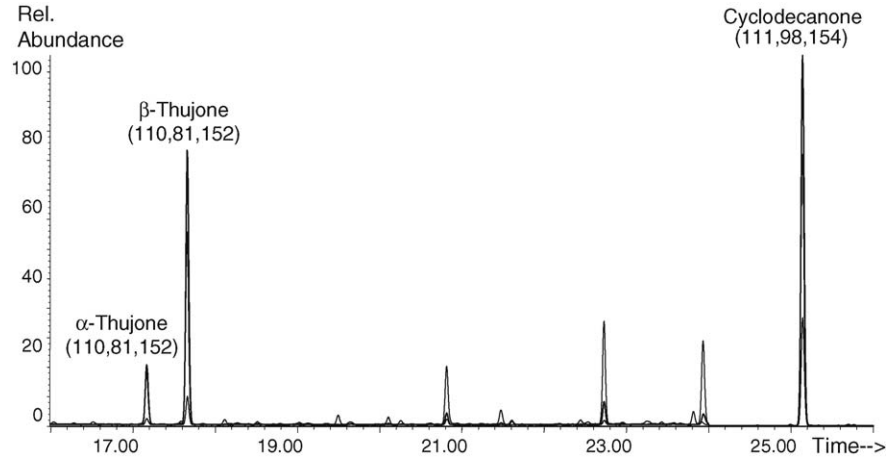

Fig. 2. GC–MS–SIM chromatogram of a self-produced Swiss Absinthe of Pontarlier containing 0.6 mg/l of α-thujone and 2.6 mg/l of β-thujone.

Table 2
Validation results

	LOD[a] (mg/l)	LOQ[a] (mg/l)	Precision[b] intraday (%)	Precision[b] interday (%)	Linearity (mg/l)	*R*
α-Thujon	0.08	0.16	1.5	2.2	0.1–40	1.000
β-Thujon	0.08	0.16	1.6	2.3	0.1–40	1.000

[a] Limit of detection and quantitation were determined by establishing a specific calibration curve from samples containing the analyte in the range of LOD. The limits were calculated from the residual standard deviation of the regression line.
[b] Precisions are expressed as R.S.D. (%), intraday ($n = 6$), interday ($n = 18$).

described above. Peak purity and selectivity, intra- and interday precision were determined. The linearity of the calibration curve was evaluated between 0.1 and 40 mg/l. For the determination of the limit of detection (LOD) and the limit of quantitation (LOQ) a separate calibration curve in the range of LOD (0.05–0.5 mg/l) was established [21,22].

3. Results and discussion

3.1. Validation

For determining thujone in absinthe, an extractive sample preparation is obligatory, because bitter spirits can contain up to 200 different components even after preparation by distillation [23]. It can happen that other components can co-eluate with α- and β-thujone, so that it is, therefore, not advisable to do without mass spectrometric detection [24]. For this reason, a fast and easy liquid–liquid extraction with subsequent GC–MS analysis was validated in this study. A typical chromatogram is shown in Fig. 2. The validation results are presented in Table 2. The calibration curves were constructed from peak areas using the SIM mode and show a linear relationship for both α- and β-thujone with coefficients of correlation of 1.000. The linear range between 0.1 and 40 mg/l covers the thujone concentrations typically found in absinthes.

The limits of detection and quantitation were 0.08 and 0.16 mg/l, respectively. By use of cyclodecanone (Fig. 1) as internal standard, which was proposed by Kröner et al. [25] for the determination of thujone in absinthe, excellent precision with ranges between 1.5–1.6% (intraday) and 2.2–2.3% (interday) was achieved.

3.2. Thujone concentrations of self-produced absinthes after historic recipes

The thujone content of historic absinthe is largely unknown and speculated to be as high as 260 mg/kg [15,16]. Hutton points out that the thujone content could be overestimated because of the insufficient analytical methods that were available at the time [16]. Historically applied methods for the determination of thujone in absinthe were based upon iodometric titration, colour reactions or paper chromatography and sometimes provided only detection limits as high as, e.g. 20 mg/l and were, therefore, unfit for the sensitive detection of small quantities [26–29]. At the beginning of the 19th century, the most modern methods were based upon the reaction of thujone with sodium nitroprusside, sodium hydroxide and acetic acid and provided a limit of detection of 5 mg/l [30–33]. However, this colour reaction was highly unspecific and therefore other essential oils, aldehydes and ketones led to a similar reaction as thujone. Even by the use of improved sample preparation, it was not possible to avoid these interferences. A positive reaction in case of the thujone analysis could not automatically be interpreted in such a way as to say that the spirit drink in question was made with wormwood herb. However, a negative result was regarded as a proof for the absence of wormwood oil [30,31]. Wilson estimated in 1936 that absinthe made from essences contained 1.8–45 mg/l, and absinthe made with wormwood herb contained 2–34 mg/l of thujone [32].

Table 3
Thujone content of absinthes produced according to historic recipes

	Swiss Absinthe of Pontarlier		White Swiss Absinthe		Absinthe of Neufchatel	
	α-Thujone (mg/l)	β-Thujone (mg/l)	α-Thujone (mg/l)	β-Thujone (mg/l)	α-Thujone (mg/l)	β-Thujone (mg/l)
Wormwood 1	nd	0.6	nd	0.7	nd	0.4
Wormwood 2	0.6	2.6	0.8	3.5	nd	1.0
Wormwood from own cultivation	nd	nd	nd	nd	nd	nd

nd: not detected.

Table 4
Thujone content of a historic absinthe and Swiss absinthes from traditional small distilleries

	α-Thujone (mg/l)	β-Thujone (mg/l)
Historic absinthe (Pernod Tarragona approximately 1930)	0.5	1.3
Swiss fée verte 58 (white absinthe)	0.4	9.0
Swiss fée verte 35 (white absinthe)	0.3	1.4

To acquire scientific based information about the thujone content of absinthes made after historic recipes, such products were prepared and analysed using a modern chromatographic method. The analysis results for the different recipes are shown in Table 3. In regard of the speculations given above, it was a bit unexpected that our absinthes contained only very low concentrations of thujone with the α-isomer up to 0.8 mg/l and the β-isomer up to 3.5 mg/l. The total thujone content was 1.3 ± 1.6 mg/l (range: 0–4.3 mg/l). Interestingly, the wormwood chemotype of our own cultivation was obviously thujone-free and, therefore, ideally suited to produce absinthe with wormwood quantities on the basis of the traditional recipes, without the producer facing the risk of exceeding the thujone limit.

3.3. Thujone concentrations of vintage absinthes

In consideration of the analysis results of the self-made absinthes, it was not unexpected that the vintage absinthe from Tarragona also contained a relatively low content of 0.5 mg/l of α-thujone and 1.3 mg/l of β-thujone. The Swiss absinthes from traditional distilleries also contained thujone well below the maximum limit (Table 4).

Our result that historic absinthes may have contained only low amounts of thujone is verified by analysis results of vintage absinthes in the literature (Table 5). Hutton found 6 mg/l of thujone in a Pernod absinthe from 1900 [16]. Schaefer et al. [34] found so low thujone concentrations analysing a legal French absinthe dating of 1904 that the authors even proposed the ''toxicological rehabilitation'' of absinthe. All in all, Hutton's hypothesis that the thujone content of vintage absinthes had been overestimated was verified by our results.

Table 5
Thujone contents of historic absinthes

Absinthe	Thujone (mg/l)	Year of analysis	Method
French 1904 (Ref. [34])	<0.01	1994	GC
Pernod fils circa 1900 (Ref. [16])	6	2002	GC
Pernod Tarragona approximately 1930	1.8	2004	GC–MS

Table 6
Classification of thujone content of commercial absinthes from different studies

Study	Classification of total thujone content (mg/kg)			
	<2	2–10	10–35	>35
Lang et al. [35] ($n = 30$)	16 (53)	9 (30)	2 (7)	3 (10)
Kröner et al. [36] ($n = 14$)	5 (37)	3 (21)	3 (21)	3 (21)
Emmert et al. [24] ($n = 16$)	7 (44)	5 (31)	4 (25)	0 (0)
CVUA Karlsruhe ($n = 87$)	53 (61)	17 (20)	16 (18)	1 (1)
All studies ($n = 147$)	81 (55)	34 (23)	25 (17)	7 (5)

Values in parenthesis are in percent.

3.4. Thujone concentrations of absinthe from current trade

Table 6 presents the results of four recently conducted studies of the thujone content of commercially available absinthe and includes own results determined by the CVUA Karlsruhe [24,35,36]. In conclusion, it can be noted that the majority of the examined samples (95%) did not exceed the thujone EU maximum limit of 35 mg/l. Strikingly, more than half of the examined samples (55%) contained less than 2 mg/l thujone.

It is, however, interesting to note that in 22% of the commercial samples thujone concentrations of more than 10 mg/l were found. Some commercial samples of today appear to have a higher concentration than the historic absinthes. This may be due to the questionable tendency of some absinthe manufacturers and suppliers to advertise the proclaimed thujone content and supposed psychoactive properties of their products on their Internet pages. Slogans such as ''contains the maximum allowed thujone concentration of 35 mg/l'' should be critically judged by the appropriate authorities. In addition, absinthe is often misleadingly advertised as having a cannabis-like effect. This is based on a hypothesis from 1975 that because of structural similarities between thujone and tetrahydrocannabinol, both substances might activate the same receptor in the central nervous system [37], which later could not be proven in experiments [38].

3.5. Influence of storage on thujone content of absinthe

In this study, the effect of storage on the thujone concentration of absinthe was studied for the first time using accelerated aging at elevated temperature and using high doses of UV light. The thermal exposure of absinthes had no statistically significant influence on the thujone concentrations (Fig. 3). In model experimental systems of ethanolic solutions, thujone was also found to be very stable under variable temperature conditions up to 100 °C [39]. On the other hand, the UV light irradiation of a commercial absinthe leads to a significant linear decrease of β-thujone from 9.7 mg/l down to 1.8 mg/l after 25 h (Fig. 4). The unusually rapid photolysis of thujone into carbon monoxide and

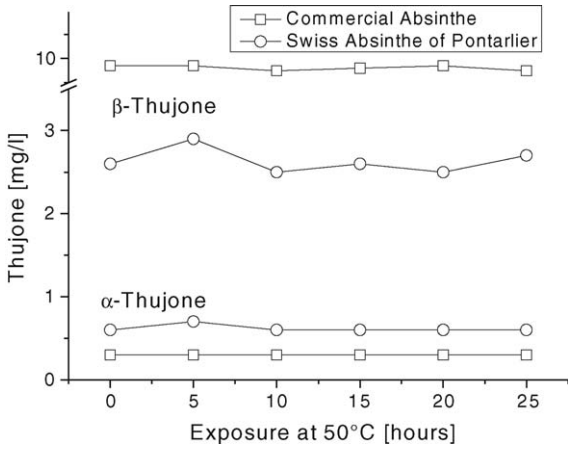

Fig. 3. Influence of elevated temperature on the thujone content of absinthe.

2-isopropyl-1,4-hexadiene on exposure to ultraviolet radiation was already described by Eastman et al. [40] with no difference in the rate between α- and β-thujone. In our case, however, the α-thujone content of both products was not significantly changed by UV irradiation. The β-thujone concentration of the self-produced absinthe with the Swiss recipe of Pontarlier also did not show a decrease. This may be explained by a content of natural antioxidants extracted from the plant material (e.g. polyphenolics). No significant change in both thujone isomers could be determined in the absinthes stored for one year at ambient temperature. In summary, it can be concluded that the thujone content of absinthe stays relatively constant during normal storage. Only at unrealistically high UV levels a decrease is possible. This influence, however, can be neglected in evaluation of the vintage absinthes, because such products are usually filled in UV resistant dark-green bottles and are stored lightproof in wine cellars.

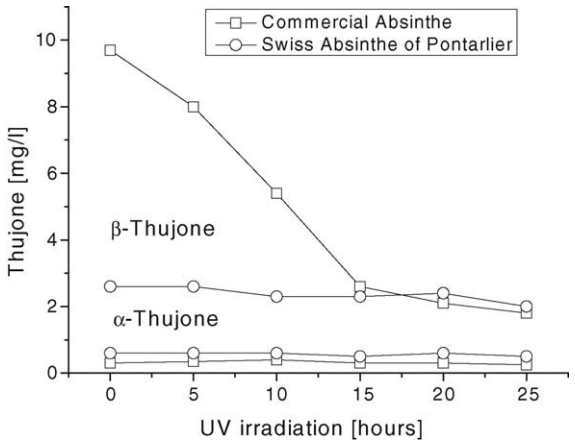

Fig. 4. Influence of UV irradiation on the thujone content of absinthe.

3.6. Food toxicological aspects

The German federal institute for risk assessment [41] holds the view that even if the legal limit of 35 mg/kg is significantly exceeded, the consumer does not ingest health-threatening amounts of thujone. Because of the high alcoholic strength, the institute advised against a continuous and massive consume. Threatening thujone concentration can only occur if beverages are made following recipes retrieved from the Internet, which suggest the use of huge amounts of wormwood oil. Some absinthe types with content of 100 mg/kg thujone were legally available in the Czech Republic until its recent integration into the EU. Weisbord et al. [42] described a case of accidental thujone intoxication in a man after having consumed a large dose of wormwood oil under the erroneous belief it had been absinthe. The symptoms were seizures, rhabdomyolysis, and acute renal failure. The wormwood oil was ordered from a website that sold essential oils for aromatherapy. This inadequate control of access to potentially unsafe herbal products is seen as an unacceptable health risk to consumers [43].

Only little valid data are available concerning the effect of α-/β-thujone, especially in regard to the influence on the central nervous system after absinthe consumption. A recent study of Dettling et al. [44] showed that the administration of alcohol containing a high concentration of thujone (100 mg/l) had a negative effect on attention performance. When the subjects were under the influence of alcohol or were administered both alcohol and low thujone concentrations (10 mg/l), these effects were not observed. Similarly, it was found that only high concentrations of thujone could temporarily counteract the anxiolytic effect of alcohol.

It is possible to explain these effects, because of an interaction of α-thujone with γ-amino butyric acid (GABA) dependent chloride channels [45–48] as well as with 5-HT_3 receptor activity [49] was demonstrated.

Very few data exist about the pharmacology of thujone. Max [50] pointed out that the typical 2–4 mg of thujone consumed per drink were far below the level at which acute pharmacological effects are observed. This is confirmed by Hinkelbein [51], who states that by the consume of absinthe, up to a blood alcohol concentration (BAC) of 2.5 g/l, approximately 3.5 mg of thujone are ingested (0.005 mg/kg bodyweight). In this order of magnitude it is highly improbable that central effects can be caused by thujone. Roth [52] calculated that to reach an effective dose of 10 mg/kg bodyweight, 2 l of an absinthe containing 400 mg/l thujone must be consumed, which would be lethal due to ethanol intoxication (BAC $>$ 5 g/l). A pilot drinking study by Kröner et al. [36] resulted in high blood alcohol concentration, but as expected no thujone was detected. The probands examined did not show a central effect caused by the terpenoids besides the effect of the alcohol. Therefore, the hallucinogenic potency of absinthe can be neglected, if the EU limit is obeyed.

4. Conclusion

In spite of our experiments, it is still extremely difficult to answer the question if thujone was responsible for absinthism. Regarding the vintage absinthes, it can only be estimated that the thujone contents were not changed during storage. Nothing is known about the toxicity or mutagenicity of the degradation product, which may have been formed by photolysis of thujone.

The self-produced products are based on currently available wormwood herb. The thujone content of wormwood herb from the 18th and 19th centuries is unknown, so that only limited conclusions can be drawn too. However, nothing in our study suggested that historic absinthes had such high thujone contents to cause toxic effects. On the contrary, the historic products complied with today's maximum limits derived to exclude hallucinogenic or other unwanted effects. Taking into account the very plausible argumentation of Strang et al. [17] that much of the syndrome of absinthism was actually acute alcohol intoxication, we deduce from our study that thujone plays none, or only a secondary role in the clinical picture of absinthism.

Therefore, the feared return of absinthism, proclaimed by some authors [7,8,14] is highly exaggerated. Absinthe is extensively controlled by the official food control and the thujone limit is obeyed by most products. Even with a slight exceedance of the limit, no toxicological effects can be expected. The effects of the recent types of absinthe are predominantly caused by the naturally high alcoholic strength (>50 vol%), which may lead today, as in the 18th century, to major health and social problems, but not being unique to absinthe.

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