Letter to the Editor

Wormwood (*Artemisia absinthium* L.) – a curious plant with both neurotoxic and neuroprotective properties?

Re: "Neuroprotective effect of Artemisia absinthium L. on focal ischemia and reperfusion-induced cerebral injury" by Bora and Sharma (*J. Ethnopharmacol* 2010;in press)

Dirk W. Lachenmeier*

Chemisches und Veterinäruntersuchungsamt (CVUA) Karlsruhe

Weissenburger Strasse 3

D-76187 Karlsruhe, Germany

* *Corresponding author.*

Tel.: +49-721-926-5434; fax: +49-721-926-5539.

E-mail address: Lachenmeier@web.de (D.W. Lachenmeier)

Conflicts of Interest: None declared.

Abstract

The medical use of the wormwood plant *Artemisia absinthium* L. dates back to at least Roman times, while during the last century this tradition was seemingly on the decline due to fears of absinthism, a syndrome allegedly caused by the wormwood-flavoured spirit absinthe and more specifically as a result of thujone, a monoterpene ketone often present in the essential oil of wormwood. If threshold concentrations are exceeded, thujone does in fact exhibit neurotoxic properties leading to dose-dependent tonic-clonic seizures in animals, likely caused by GABA type A receptor modulation. Research has shown that the concentrations of thujone present in absinthe were not sufficient to exceed these thresholds, and the marketing of wormwood-flavoured alcoholic beverages has ultimately been reinstated. The declining fears of absinthism may have led to a revival of the medical uses of wormwood, evidenced by several experimental reports, e.g. on the treatment of Crohn's disease. Most recently in this journal, neuroprotective properties of wormwood were detected in rats, and the plant was suggested to be possibly beneficial in the treatment of strokes. While these results sound promising and worthwhile for further investigation, the well-defined profile of adverse properties of wormwood demands a more cautious interpretation of these results. It remained unclear in the studies, for example, if the threshold dose for thujone (e.g. as set by EMEA) would be exceeded during therapeutic usage. Due to the colourful history of wormwood, its application in humans should be preceded by a thorough and careful risk-benefit analysis.

Keywords: Artemisia absinthium L., wormwood, absinthe, thujone, neurotoxicity syndromes, seizures, neuroprotectants

1. Introduction

The wormwood plant *Artemisia absinthium* L., which features the monoterpene ketone thujone as its possible "active ingredient" is certainly of ethnopharmacological interest. Its documented medical use can be dated back to the Ebers Papyrus, an ancient Egyptian medical document dating from about 1552 B.C. and the oldest preserved medical document (Anon., 1937). This papyrus is believed to be a copy of the ancient books of Thoth (3500 B.C.). The name “wormwood” is derived from its anthelmintic properties, which were recognized by the ancient Egyptians (Padosch et al., 2006). Wormwood, in the context of its bitter taste, is mentioned several times in the bible (Deu 29:18; Pro 5:4; Jer 9:15; Amo 5:7; Rev 8:11; Lam 3:15). The Greek word *apsinthion*, meaning "undrinkable", is likely the ancestor of the word absinthe, which is used in French for the plant species as well as for the alcoholic beverage (Padosch et al., 2006). The Greek mathematician and philosopher, Pythagoras of Samos (569-475 B.C.), recommended wine-soaked wormwood leaves to alleviate labour pains; Hippocrates (~460-377 B.C.) used wormwood extracts for the treatment of menstrual pain and rheumatism (Baker, 2001).

Pliny the Elder (23-79), a Roman scholar and scientist, also mentioned extracts of wormwood in his opus *Historia Naturalis* (Pliny the Elder, 1855; Nathan-Maister, 2008). In the Middle Ages, wormwood was used as a purge and vermifuge, and it developed towards a “general remedy for all diseases” and was referred to as “a herb of Mars” for its overarching medical powers (Baker, 2001). Wormwood’s bitter taste inspired women to apply it to their nipples to encourage the weaning of their babies. In fact, Shakespeare has Juliet’s nurse expound upon this in *Romeo and Juliet* (Padosch et al., 2006).

Whilst wormwood is mentioned in almost all early herbals, the comprehensive section on wormwood contained in Rembert Dodoen's herbal "The Stirpium Historiae" printed in 1583 is particularly noteworthy (Nathan-Maister, 2008). The only book exclusively devoted to the subject appears to be the "Herba picra, vel de absinthio analecta ad normam & formam academiae naturae curiosorum" published in 1667 (Fehr, 1667).

2. The rise and fall of absinthe

In the 18th century, alcoholic decoctions of wormwood and other plants were used as all-purpose remedies or "cure-alls", but it was not until the beginning of the 19th century that the wormwood-flavoured alcoholic extracts and distillates were seen not only as patent medicines, but also as aperitifs, and the large scale production of absinthe began (Nathan-Maister, 2008). During the French occupation of Algeria, absinthe was still used more as medicine than as recreational beverage, and it was given to the troops as preventive measure for helminthiasis or fevers, and when mixed with water it was believed to kill germs and fend off dysentery (Padosch et al., 2006; Nathan-Maister, 2008). When the returning troops brought with them the taste for the refreshingly bitter drink, absinthe became a hit in bars and bistros all over France, and at the peak years between 1880-1910, absinthe was conceived and marketed purely as an alcoholic beverage (Lanier, 1995; Padosch et al., 2006; Nathan-Maister, 2008). The annual per capita consumption of absinthe in France increased fifteen-fold between 1875 and 1913. According to an article in The Times (1915), French consumption of pure alcohol in 1876 was 15,500 hectolitres; it was 10 times that amount in 1908, and in 1913 it had reached the figure of 239,492 hectolitres, representing 60 litres per inhabitant. Corresponding to this mass consumption, chronic use of absinthe was claimed to produce a syndrome called absinthism, which was characterized by addiction, hyperexcitability, epileptic fits and hallucination (Padosch et al., 2006; Nathan-Maister, 2008). The definition of absinthism as a particular syndrome separate from alcoholism is directly attributable to the French physician Valentin Magnan (Dowbiggin, 1996; Luauté, 2007; Eadie, 2009). In Magnan's studies on absinthism between 1864 and 1874, he described visual and auditory hallucinations accompanied by alterations in consciousness after the consumption of absinthe (Magnan, 1864; Magnan, 1874). Wormwood, the major ingredient of absinthe, was quickly pronounced to be the culprit. This was predominantly based on animal experiments conducted with pure wormwood extract (Padosch et al., 2006). If injected in its pure form, wormwood extracts and alcohol showed distinctly different symptoms (Magnan, 1874; Ott, 1892; Boyce, 1895; Cunningham, 1898; Lesieur, 1907;

Ossipow, 1914). These early investigations and the resultant systematic experiments with pure thujone (see below) have consistently shown that wormwood may act as a strong agent causing seizures in animals. The only issue was that the dose-response relationship was largely neglected, as later investigations have shown that the wormwood content in absinthe was so negligible that the "no effect level" in animal experiments with additional safety factors would not have been exceeded by even excessive human absinthe ingestion (Lachenmeier et al., 2008). The most plausible hypothesis today is that absinthism was just misdiagnosed alcoholism, as ethanol alone can explain all of absinthe's alleged effects (Strang et al., 1999; Padosch et al., 2006; Lachenmeier et al., 2010).

3. The medical use of wormwood - a collateral damage of the absinthe prohibition?

In the time of the absinthe prohibition, which lasted from 1915 till 1988 in most European countries (Padosch et al., 2006), the medical use and ethnopharmacological research of wormwood was apparently hindered by the demonization of the plant; although the absinthe laws generally regulated only the manufacture, importation, distribution and sale of absinthe (i.e. the alcoholic beverage) and not the wormwood herb itself, and did not specifically disallowed the medical use of wormwood. This is evidenced, for example, by the lack of published studies researching the potential therapeutic uses and the molecular mechanisms behind the ethnologically known properties of the plant in the years during the prohibition. The fear of absinthism in connection with the medical use of wormwood is also still evinced by the recently published monograph of the European Medicines Agency (EMEA, 2009). The EMEA has proposed maximum daily intakes for wormwood based on the presence of its constituent thujone. The daily intake of 3.0 mg/person is seen as acceptable for a maximum duration of two weeks. It is striking that the EMEA rationale for establishing such a limit is based on a study regading the attention performance and mood under the influence of thujone and alcohol (Dettling et al., 2004). The results of this study, in which the group given high thujone concentrations (in combination with alcohol) demonstrated changes in attention performance, were also used to postulate the requirement of

a warning label that states "patients should not drive or operate machinery after intake of Absinthii herba preparations" (EMEA, 2009).

Throughout history, very few anecdotal reports have been published concerning the toxicity associated with *Artemsia* overdose in humans (Smith, 1862; Smith, 1863; Robinson, 1889; Weisbord et al., 1997). The adverse properties of the thujone contained in wormwood cannot, however, be directly dismissed. The major effect reported in humans as well as in experimental animals was neurotoxicity manifested by epileptiform convulsions (Keith, 1931; Sampson and Fernandez, 1939; Wenzel and Ross, 1957; Pinto-Scognamiglio, 1967; Millet et al., 1979; Steinmetz et al., 1980; Millet et al., 1981), which had been thought to be due to γ-aminobutyric acid type A ($GABA_A$) receptor modulation of thujone (Höld et al., 2000). Several animal experiments conducted with pure thujone have confirmed its properties to cause dose-dependent tonic-clonic seizures. Besides two short-term animal experiments conducted in the 1960s with rats (Surber, 1962; Margaria, 1963; SCF, 2003), the two most recent chronic long-term studies with rats and mice are notable (NTP, 2009). The no-effect levels (NOEL) were in the range between 5 and 12.5 mg/kg bodyweight/day (SCF, 2003). As previously mentioned, the consumption of absinthe was unable to reach the NOEL (Lachenmeier et al., 2008). Currently, it is relatively unclear how much thujone is present in medically used wormwood preparations. Wide variations are expected due to the natural thujone variation in wormwood (0-71% thujone in the essential oil of wormwood, see review in Lachenmeier and Nathan-Maister (2007)) as well as the amount extracted during preparation, e.g. infusion of wormwood tea. Thujone is less soluble in water than in ethanol, and according to Tegtmeier and Harnischfeger (1994), only 8% of thujone is recovered in water compared to extraction in 90% vol ethanol. However, there is a complete lack of data in the literature regarding the actual thujone content in herbal medicines. As the literature reports only few cases of wormwood intoxication, generally due to the accidental or intentional ingestion of very large amounts of wormwood oil, the occasional therapeutic use of wormwood preparations appears to be of rather low likelihood to result in

acute toxic events. For wormwood itself, only short-term toxicity studies are available (a 13-week study by Muto et al. (2003) and a six-month study reported by Omer et al. (2007)), both of which failed to show any adverse effects. However, uncertainty remains as the thujone content in the wormwood material used in both toxicity studies was inadequately characterized. In the Muto et al. (2003) study, the composition of the wormwood extract was stated to be unknown. In the Omer et al. (2007) study, the thujone content was less than 5 ppm (no exact value stated). The experience from beverage production shows that the thujone content in wormwood is highly variable, depending not only on the plant's chemotype, but also on time of harvest, climate and drying conditions (Lachenmeier et al., 2006). Similar to food producers, manufacturers of herbal wormwood preparations should apply quality control measures to ensure that toxicity studies conducted with low thujone chemotypes of wormwood are representative of the batches actually sold.

4. Comment on modern studies about wormwood

Regarding the well-known neurotoxic properties of wormwood, the headline of the article by Bora and Sharma (2010) that wormwood has neuroprotective effects on focal ischemia and reperfusion-induced cerebral injury was rather surprising. The results, which were based on animal experiments, sound promising and will hopefully lead to a renaissance of research on wormwood aimed at validating the ethnological and traditional uses of the plant. Promising results relating to the therapeutic uses of wormwood were also obtained in previous studies on Crohn's disease (Omer et al., 2007; Krebs et al., 2010). Wormwood has also exhibited hepatoprotective action (Gilani and Janbaz, 1995).

Prior to clinical studies in humans, however, the above mentioned adverse properties of wormwood should be more carefully evaluated. The surprising disparity between the neurotoxic and neuroprotective effects of the plant was not mentioned in the study of Bora and Sharma (2010). The thujone concentration in the applied wormwood plant extract was not stated in the study, so that it is not possible to pass judgment in terms of the exceedance of the NOEL or the EMEA guidelines. It

could very well be the case that thujone was removed during the relatively extended preparation of the wormwood extract, which included drying and milling of the plant parts, followed by methanolic Soxhlet extraction, vacuum reduction and freeze drying. Therefore, a limitation of the study is that the neuroprotective effects do not apply to wormwood per se (as could be erroneously deduced from the title), but only to the extract prepared in this specific fashion.

In conclusion, the risk associated with the occasional medicinal use of wormwood appears to be rather low, however, due to its colourful history, the application in humans should be preceded by a careful risk-benefit analysis, especially considering the toxic properties of thujone.

References

Anon., 1937. The Papyrus Ebers: The greatest Egyptian medical document translated by B. Ebell. Levin & Munksgaard, Copenhagen.

Baker, P., 2001. The book of absinthe: a cultural history. Grove Press, New York, USA.

Bora, K.S., Sharma, A., 2010. Neuroprotective effect of *Artemisia absinthium* L. on focal ischemia and reperfusion-induced cerebral injury. Journal of Ethnopharmacology in press. DOI: 10.1016/j.jep.2010.04.030.

Boyce, R., 1895. A Contribution to the study of descending degenerations in the brain and spinal cord, and of the seat of origin and paths of conduction of the fits in absinthe epilepsy. Philosophical Transactions of the Royal Society of London 186, 321-382.

Cunningham, R.H., 1898. The restoration of coordinated, volitional movement after nerve "crossing". American Journal of Physiology 1, 239-254.

Dettling, A., Grass, H., Schuff, A., Skopp, G., Strohbeck-Kuehner, P., Haffner, H.T., 2004. Absinthe: attention performance and mood under the influence of thujone. Journal of Studies on Alcohol 65, 573-581.

Dowbiggin, I., 1996. Back to the future: Valentin Magnan, French psychiatry, and the classification of mental diseases, 1885-1925. Social History of Medicine 9, 383-408.

Eadie, M.J., 2009. Absinthe, epileptic seizures and Valentin Magnan. The Journal of the Royal College of Physicians of Edinburgh 39, 73-78.

EMEA, 2009. Community herbal monograph on Artemisia absinthium L., herba. European Medicines Agency, London, UK.

Fehr, J.M., 1667. Hiera picra, vel de absinthio analecta, ad normam & formam academiae naturae curiosorum selecta. Jacob Trescher, Leipzig, Germany.

Gilani, A.H., Janbaz, K.H., 1995. Preventive and curative effects of *Artemisia absinthium* on acetaminophen and CCl4-induced hepatotoxicity. General Pharmacology 26, 309-315.

Höld, K.M., Sirisoma, N.S., Ikeda, T., Narahashi, T., Casida, J.E., 2000. α−Thujone (the active component of absinthe): γ-aminobutyric acid type A receptor modulation and metabolic detoxification. Proceedings of the National Academy of Sciences of the United States of America 97, 3826-3831.

Keith, H.M., 1931. The effect of various factors on experimentally produced convulsions. American Journal of Diseases of Children 41, 532-543.

Krebs, S., Omer, T.N., Omer, B., 2010. Wormwood (*Artemisia absinthium*) suppresses tumour necrosis factor alpha and accelerates healing in patients with Crohn's disease - A controlled clinical trial. Phytomedicine 17, 305-309.

Lachenmeier, D.W., Nathan-Maister, D., 2007. Systematic misinformation about thujone in pre-ban absinthe. Deutsche Lebensmittel-Rundschau 103, 255-262.

Lachenmeier, D.W., Nathan-Maister, D., Breaux, T.A., Luauté, J.-P., Emmert, J., 2010. Absinthe, absinthism and thujone. New insight into the spirit's impact on public health. Open Addiction Journal 3, 32-38.

Lachenmeier, D.W., Walch, S.G., Padosch, S.A., Kröner, L.U., 2006. Absinthe - A review. Critical Reviews in Food Science and Nutrition 46, 365-377.

Lachenmeier, D.W., Nathan-Maister, D., Breaux, T.A., Sohnius, E.M., Schoeberl, K., Kuballa, T., 2008. Chemical Composition of Vintage Preban Absinthe with Special Reference to Thujone, Fenchone, Pinocamphone, Methanol, Copper, and Antimony Concentrations. Journal of Agricultural and Food Chemistry 56, 3073-3081.

Lanier, D., 1995. Absinthe-the cocaine of the nineteenth century: a history of the hallucinogenic drug and its effect on artists and writers in Europe and the United States. McFarland, Jefferson, North Carolina, USA.

Lesieur, C., 1907. Nouvelles Recherches sur la toxicité expérimentale des essences usuelles. Archives de Médecine Expérimentale et d'Anatomie Pathologique 18, 803-817.

Luauté, J.P., 2007. L'absinthisme: la faute du docteur Magnan [Absinthism: the fault of doctor Magnan]. L'Evolution Psychiatrique 72, 515-530.

Magnan, V., 1864. Accidents déterminés par l'abus de la liqueur d'absinthe. L'Union Médicale 92&94, 227-232-257-262.

Magnan, V., 1874. On the comparative action of alcohol and absinthe. The Lancet 104, 410-412.

Margaria, R., 1963. Acute and sub-acute toxicity study on thujone. Unpublished report. Istituto di Fisiologia, Università di Milano. Cited from SCF (2003).

Millet, Y., Jouglard, J., Steinmetz, M.D., Tognetti, P., Joanny, P., Arditti, J., 1981. Toxicity of some essential plant oils. Clinical and experimental study. Clinical Toxicology 18, 1485-1498.

Millet, Y., Tognetti, P., Lavaire-Perlovisi, M., Steinmetz, M.D., Arditti, J., Jouglard, J., 1979. Experimental study of the toxic convulsant properties of commercial preparations of essences of sage and hyssop. Revue d'électroencephalographie et de neurophysiologie clinique 9, 12-18.

Muto, T., Watanabe, T., Okamura, M., Moto, M., Kashida, Y., Mitsumori, K., 2003. Thirteen-week repeated dose toxicity study of wormwood (*Artemisia absinthium*) extract in rats. The Journal of Toxicological Sciences 28, 471-478.

Nathan-Maister, D., 2008. The Absinthe Encyclopedia. Oxygéneé Press, Burgess Hill, UK.

NTP, 2009. TR-570 - alpha/beta thujone mixture: Pathology tables, survival and growth curves from NTP long-term studies. The National Toxicology Program, Research Triangle Park, NC, USA.

Omer, B., Krebs, S., Omer, H., Noor, T.O., 2007. Steroid-sparing effect of wormwood (Artemisia absinthium) in Crohn's disease: a double-blind placebo-controlled study. Phytomedicine 14, 87-95.

Ossipow, W.P., 1914. Über die Dosierung der Absinthessenz (essence d'absinthe cultivée) beim Hervorrufen von Anfällen experimenteller Epilepsie bei Hunden. Monatsschrift für Psychiatrie und Neurologie 85, 516-525.

Ott, I., 1892. The seat of absinthic epilepsy. The Journal of Nervous and Mental Disease 19, 696-698.

Padosch, S.A., Lachenmeier, D.W., Kröner, L.U., 2006. Absinthism: a fictitious 19th century syndrome with present impact. Substance Abuse Treatment, Prevention, and Policy 1, 14.

Pinto-Scognamiglio, W., 1967. Connaissances actuelles sur l'activite pharmacodynamique de la thuyone, aromatisant naturel d'un emploi etendu [Current knowledge on the pharmacodynamic activity of the prolonged administration of thujone, a natural flavoring agent]. Bollettino Chimico Farmaceutico 106, 292-300.

Pliny the Elder, 1855. Book XXVII. Chap. 28. Absinthium or wormwood. in: Bostock, J. and Riley, H.T. (Eds.), The natural history. Taylor and Francis, London, UK

Robinson, B., 1889. The toxic effects of wormwood. The Lancet 133, 770.

Sampson, W.L., Fernandez, L., 1939. Experimental convulsions in the rat. Journal of Pharmacology and Experimental Therapeutics 65, 275-280.

SCF, 2003. Opinion of the Scientific Committee on Food (SCF) on Thujone. http://ec.europa.eu/food/fs/sc/scf/out162_en.pdf (accessed on 2010/02/08).

Smith, W., 1862. A case of poisoning by oil of wormwood (Artemisia absinthium). The Lancet 80, 619.

Smith, W., 1863. Case of poisoning by oil of wormwood (Artemisia absinthium). Medico-Chirurgical Transactions 46, 23-24.

Steinmetz, M., Tognetti, P., Mourogue, M., Jouglard, J., Miller, Y., 1980. Sur la toxicité de certaines huiles essentielles du commerce: essence d'hysope et essence de sauge. Plantes Medicinales et Phytotherapie 14, 34-45.

Strang, J., Arnold, W.N., Peters, T., 1999. Absinthe: what's your poison? British Medical Journal 319, 1590-1592.

Surber, W., 1962. Etude de toxicité sous-chronique de la thujone sur rats. Rapport final. Institute Battelle, Genève, Switzerland. Cited from SCF (2003).

Tegtmeier, M., Harnischfeger, G., 1994. Methods for the reduction of thujone content in pharmaceutical preparations of *Artemisia*, *Salvia* and *Thuja*. European Journal of Pharmaceutics and Biopharmaceutics 40, 337-340.

The Times, 1915. The conquest of absinthe - French national curse suppressed. The Times, Issue 40819 Apr 03, 7.

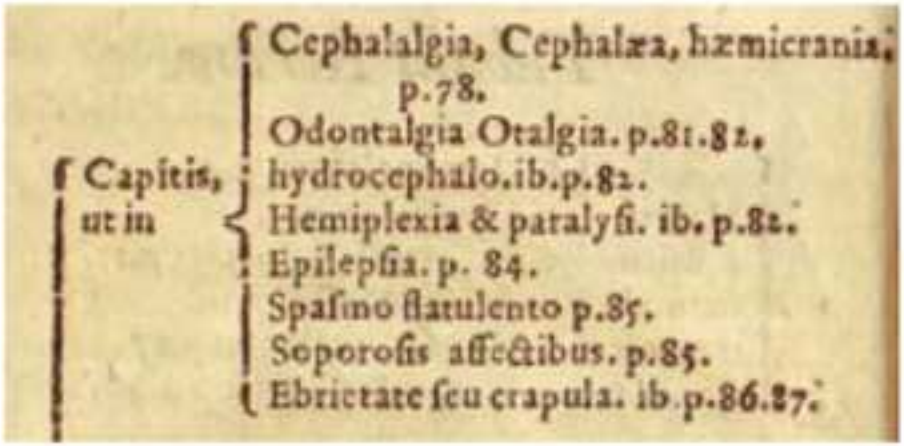
Weisbord, S.D., Soule, J.B., Kimmel, P.L., 1997. Poison on line - acute renal failure caused by oil of wormwood purchased through the Internet. The New England Journal of Medicine 337, 825-827.

Wenzel, D.G., Ross, C.R., 1957. Central stimulating properties of some terpenones. Journal of the American Pharmaceutical Association 46, 77-82.

Graphical Abstract

Click here to download high resolution image


HIERA PICRA,
DE
ABSINTHIO
ANALECTA,
JOH. MICHAELE FEHR, D.


Capitis, ut in
- Cephalalgia, Cephalæa, hæmicrania, p.78.
- Odontalgia Otalgia. p.81.82.
- hydrocephalo. ib. p.82.
- Hemiplexia & paralysi. ib. p.82.
- Epilepsia. p. 84.
- Spasmo flatulento p.85.
- Soporosis affectibus. p.85.
- Ebrietate seu crapula. ib. p.86.87.