Christmas Gingerbread (*Lebkuchen*) and Christmas Cheer – Review of the Potential Role of Mood Elevating Amphetamine-like Compounds Formed *in vivo* and *in furno*

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Abstract: The typical spices used in winter include nutmeg, cinnamon, clove and anise. These spices contain two groups of chemicals, the allylbenzenes and their isomers, the propenylbenzenes. It was suggested 40 years ago by Alexander Shulgin that these substances act as metabolic precursors of amphetamines. The biotransformation of these precursors to nitrogen-containing metabolites is reviewed. These reactions have not been reported in humans. Whether or not the pharmacology and toxicology of spices such as nutmeg can be explained on the basis of their allylbenzene or propenylbenzene content is speculative. Humans may be exposed to amphetamines derived from these precursors *in forno*, the formation during baking and cooking, for example in the preparation of *Lebkuchen*, or Christmas gingerbread. It is possible that this may be responsible, in part, for uplifting our mood in winter. However, the role of these aromatic substances, acting simply as odours, evoking old memories of winters past, cannot be ignored. Whether spices have a true pharmacological effect or they act as aromatherapy remains to be elucidated through clinical and laboratory studies.

Key words: Allylbenzenes – Propenylbenzenes – Amphetamines – Spices – Winter – Gingerbread – Odour

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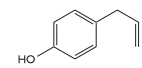
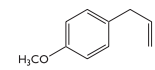
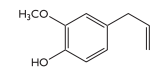
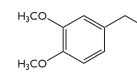
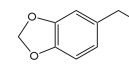
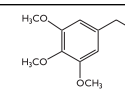
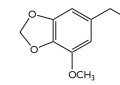
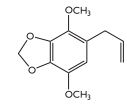
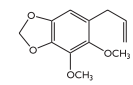
Introduction

In European cultures, the celebrations of mid-summer and mid-winter are dramatically different with respect to dietary preferences. The clean tastes of fresh fruit and iced drinks in the warm air and under a bright summer sun are exchanged in the dark mid-winter by the heavy odours and flavours of foreign spices that permeate from hot wine (*Glühwein, svařené víno*), gingerbread biscuits (*Lebkuchen, perník*) and dark rich fruit cakes. Recalling the salad days of summer or Christmas and New Year celebrations evokes such different memories that we are bound to ask if the striking divergence of summer and winter moods is not merely due to differences of climate and daylight, but includes a contribution from the seasonal diet. Nations have fought wars and colonised foreign lands at enormous expense

Table 1 – Naturally-occurring allylbenzenes

Allylbenzene	Food source	Plant	Chemical structure	Boiling Point (°C)
Chavicol	Bay leaf	*Pimenta racemosa*		238
Estragole	Tarragon	*Artemisia dranunculus* L.		215–216
Eugenol	Clove	*Eugenia caryophylla*		254
Methyleugenol	Sweet basil	*Ocimum basilicum* L.		254–255
Safrole	Sassafras (root beer)*	*Sassafras albidum*		232–234
Elemicin	Nutmeg	*Myristica fragrans* Houtt.		
Myristicin	Nutmeg	*Myristica fragrans* Houtt.		173 [40 mm Hg]
Parsley apiol	Parsley	*Petroselinum sativum*		294
Dill apiol	Dill	*Anethum graveolens* L.		285

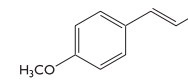
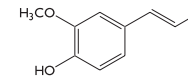
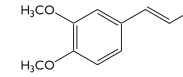
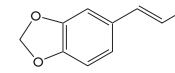
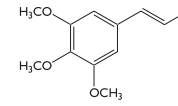
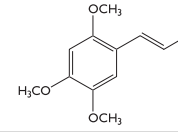
*Root beer was originally made using oil of sassafras as a flavouring (approx. 75% safrole) but today commercial sassafras oil must be safrole-free. Modern root beers tend to be flavoured with methyl salicylate (wintergreen).

to secure the domestic supply of spices. Perhaps herbs and spices have a more intimate relationship with us than it appears at first sight.

One factor that unites the vast majority of the spices used in winter foods and beverages is that they contain volatile alkenylbenzene derivatives, mainly allylbenzenes, such as eugenol (from cloves) (Table 1), and propenylbenzenes, such as (*E*)-anethole (from aniseed) (Table 2). While these are not the only classes of volatile compound that comprise the essential oils derived from the plants listed in Tables 1 and 2, the allylbenzenes and propenylbenzenes certainly are the dominant constituents. Many of the pure compounds have odours that we immediately recognise as belonging to particular spices. It will be noted that, although volatile, all these alkenylbenzenes have relatively high boiling points (b.p.). The spices, therefore, may release a pleasing odour during the cooking process, but nevertheless will retain the bulk of their constituents for subsequent ingestion.

Lebkuchen are a traditional Christmas sweet popular in Germany, Austria and Switzerland. They originate from Nürnberg in Bavaria and are sometimes referred to as Nurenberg gingerbread. The forests around Nürnberg provided the local Franconian monks with honey for the production of honey cake. In the Middle Ages, Nürnberg had a unique geographical position at the junction of the north-

Table 2 – Naturally-occurring propenylbenzenes

Propenylbenzene	Food source	Plant	Chemical structure	Boiling Point (°C)
(*E*)-Anethole	Aniseed	*Pimpinella anisum* L.		234
(*E*)-Isoeugenol	Clove	*Eugenia caryophylla*		266
(*E*)-Methyl isoeugenol	Mace	*Myristica fragrans* Houtt.		–
(*E*)-Isosafrole	Sassafras (root beer)*	*Sassafras albidum*		253
(*E*)-Isoelemicin	Nutmeg	*Myristica fragrans* Houtt.		–
(*E*)-Asarone	Carrot	*Daucus carota*		296

*See footnote to Table 1.

south and east-west trading routes and consequently enjoyed a supply of oriental spices with relative ease. It was not long before monks added spice to their honey cake, and *Lebkuchen* were born. This was, perhaps, an inevitable development, given the Church's long association with the fragrances, such as the burning of incense, and the Biblical stories of frankincense and myrrh. The humble communion wafer also played a part in the evolution of modern *Lebkuchen*, the monks placing the biscuit mix on a wafer to prevent it sticking to the oven. Typical *Nürnberger Lebkuchen* are depicted in Fig. 1.

Allylbenzenes as "essential amphetamines" – the theory

Perusal of the chemical structures of the allylbenzenes in Table 1 reveals that these chemicals are merely lacking ammonia to become amphetamines. This was first pointed out by the pioneering medicinal chemist Alexander Shulgin in the early 1960s in a series of papers in *Nature*. He was concerned initially with the dose-dependent psychotropic effects of 3,4,5-trimethoxyamphetamine (TMA), a little-known analogue of mescaline [1]. This led him to speculate [2] that TMA might be formed *in vivo* by the addition of ammonia to elemicin (Fig. 2), one of the allylbenzenes present in the essential oil derived from nutmeg (Table 1). This was offered as an explanation for the psychotropic properties of nutmeg [2]. However, myristicin (Table 1) is the principal allylbenzene in nutmeg oil, and it was then postulated that this substance too might be metabolized to an amphetamine (Fig. 2), in this case 3-methoxy-4,5-methylenedioxyamphetamine (MMDA). Shulgin then synthesized MMDA and tested it on mice, dogs and humans, reporting similar hallucinogenic properties to TMA [3]. These ideas were further elaborated [4] when the author speculated that addition of an amine, rather than ammonia, would lead to the corresponding *N*-substituted amphetamine. Moreover, it was proposed that the allylbenzenes may isomerise *in vivo* to their corresponding propenylbenzenes, for example, myristicin to isomyristicin or safrole to isosafrole (see Table 2). These propenylbenzenes were

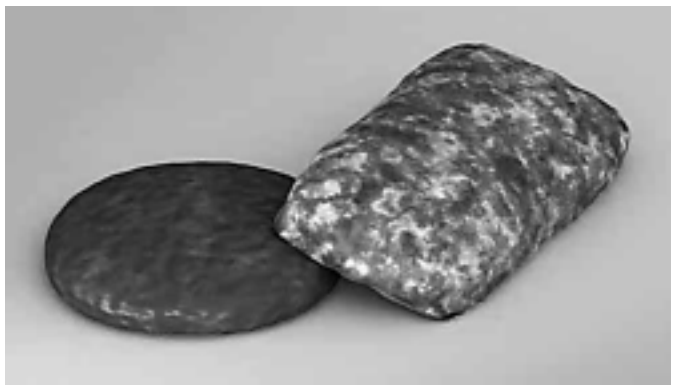


Figure 1 – Typical Nürnberger Lebkuchen.

also hypothesized to be converted to amphetamines *in vivo* [4]. Potential mechanisms for the addition of ammonia *in vivo* to propenylbenzenes were advanced, including direct addition of ammonia across the double bond, epoxidation of the double bond, followed by reaction with ammonia to yield phenylpropanolamines (ephedrine derivatives), and the action of transaminases on oxidized phenylacetone metabolites [1, 4]. In another review article [5], the possibility was considered that the intoxication syndrome associated with nutmeg may be due to the conversion of myristicin, elemicin and safrole, all to their corresponding amphetamine derivatives, the nutmeg tree (*Myristica fragrans* Houtt.) being the only plant then known to contain all three of these allylbenzenes together [5]. The authors stated, "It is entirely possible that the combination of the amines derivable from the essential oil aromatics could produce the psychological effects of nutmeg…" Finally, these authors reported the synthesis of eleven amphetamines that corresponded to nine allylbenzenes and two propenylbenzenes found in various essential oils. They reported also the testing of five of these amphetamines singly on human subjects and that the potency of the compounds relative to mescaline was 2–18%. It is worth noting that the reference compound mescaline is a powerful hallucinogen.

In their seminal textbook TIHKAL, Shulgin & Shulgin describe the allylbenzenes and propenylbenzenes in the diet as "essential amphetamines" [6], not in the meaning that they are somehow necessary, but that they occur in essential oils, the oils from plants that have an essence or odour. In a double meaning, these "essential amphetamines" are also the potential precursors of amphetamine-like substances in the body.

Allylbenzenes as "essential amphetamines" – the *in vivo* evidence

In this context, the word allylbenzenes will be taken to encompass also the isomeric propenylbenzenes, whether as found in nature or formed *in vivo* by isomerisation of allylbenzenes proper.

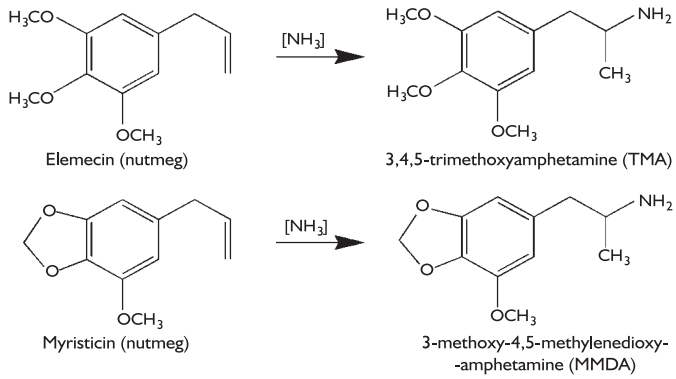


Figure 2 – The hypothetical formation of amphetamines from allylbenzenes according to Shulgin [2–4].

A number of enquiries into the metabolism of allylbenzenes in laboratory animals have addressed the question of whether or not amphetamine-like metabolites can be detected. Regrettably, no work in human subjects appears to have been published. Drawing directly on the Shulgin's work, a group from the US National Institute of Environmental Health Sciences (NIEHS) published series of reports on the metabolic potential for the formation of amphetamines from allylbenzenes. In the first of these [7], they administered myristicin, safrole, isosafrole, (*E*)-asarone, (*Z*)-asarone and dihydrosafrole to male rats (75–300 mg/kg p.o. or i.p. in safflower oil). Urine was collected daily up to 6 days and, after various solvent extractions, subjected to thin-layer chromatography (TLC). The TLC plates were subjected to various treatments, including ninhydrin, which does not give a coloured reaction with non-nitrogenous compounds. Myristicin administration yielded two ninhydrin positive spots, most prominently in the 24–48 h urines. Control safflower oil administration yielded no ninhydrin-positive spots, and the results were similar between i.p. and oral administration, suggesting that the gut flora did not make these metabolites. Rats treated with safrole gave similar results, with four ninhydrin-positive spots. (*E, Z*)-isosafrole gave results very similar to safrole. In stark contrast, dihydrosafrole, which does not contain a double-bonded side-chain,

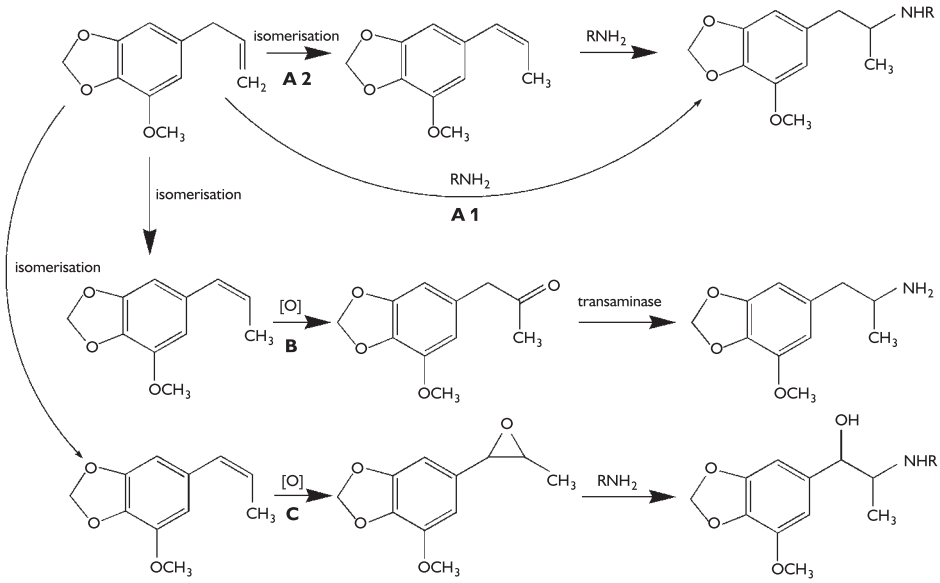


Figure 3 – Four potential biochemical mechanisms advanced by Shulgin [1, 4, 5] for the formation of amphetamine derivatives from myristicin after isomerisation to isomyristicin. Route A1 involves the direct addition of ammonia or an amine across the double bond of myristicin, and Route A2 involves prior isomerisation to isomyristicin, followed by amine addition; Route B involves oxidation to a phenylacetone derivative, followed by transamination; Route C involves epoxidation of the double bond, followed by addition of ammonia or an amine to yield a phenylpropanolamines derivative.

did not yield ninhydrin-positive spots. The greatest yield of ninhydrin-positive material was found with the *trans*-isomer of asarone, (*E*)-asarone, and this was excreted within the first 17 h post-dose. Of great interest was the finding that (*E*)-asarone produced 10–50 times more ninhydrin-positive material (three spots) than did (*Z*)-asarone (the *cis*-isomer), safrole or myristicin. The authors summarized that allylbenzenes and propenylbenzenes do give rise to nitrogen-containing metabolites in rat urine, but that these materials are unstable and give rise to ninhydrin-negative carbonyl-containing compounds. They wrote, "it is very probable that these ninhydrin-positive materials in urine are phenylisopropylamines or amphetamines which could bring about the psychotropic effect for nutmeg and other natural products that contain these constituents." These authors continued this work with elemicin and reported [8] the formation in the rat of the same three aminopropiophenones from elemicin, as found for myristicin, safrole, isosafrole, and (*E*)-asarone (Fig. 4). However, the 3,4,5-trimethoxy derivatives formed from elemicin were considerably more unstable than the corresponding metabolites of other allylbenzenes [8]. Furthermore, these same authors reported [9] that the predicted metabolites of myristicin in the rat and guinea pig, based upon their studies with elemicin [8], would include the dimethylamine addition product (see Fig. 4). None was found. However, the corresponding pyrrolidine and piperidine addition products were reported for myristicin [9]. The initial premise of these metabolic explanations was an attempt to identify and characterize amphetamine-like substances in experimental animals after allylbenzene administration, in an attempt to explain the psychopharmacological effects of nutmeg, in particular. These authors commented [9] that, whenever an intraperitoneal or oral administration of myristicin, safrole, isosafrole, (*E*)- and (*Z*)-asarone, elemicin or eugenol was made, in either rats or guinea pigs, the animals became "highly active and excited" in the first 15–30 min post-dose, thereafter the animals became "very sedated, immobile and non-responsive to sound or motion for periods up to 2 h." The implicit suggestion of these authors is

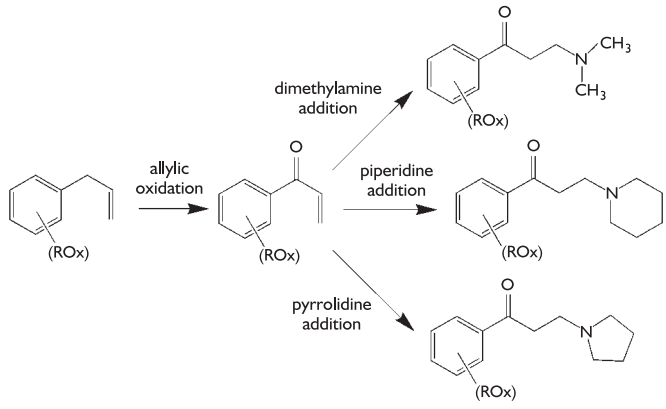


Figure 4 – Urinary nitrogen-containing metabolites of allylbenzenes in rat and guinea pig identified as tertiary aminopropiophenones.

that amphetamine-like metabolites are formed from allylbenzenes only transiently, and then converted to the observed aminopropiophenone urinary metabolites, with a corresponding alteration of pharmacological response. Other studies reported [10] also eugenol to be able to produce highly unstable aminopropiophenone urinary metabolites. Mechanism of production of the aminopropiophenone metabolites from safrole and their decomposition to non-nitrogenous products was also studied [11, 12], but it did not cast further light on the occurrence of transient amphetamines or on the observed pharmacological response to administered allylbenzenes. As this story continued in the NIEHS laboratory, an interesting observation was made, that preparations of monoamine oxidase (MAO) from different organs, specifically, rat brain, liver and kidney mitochondrial MAO, was differentially inhibited by the three aminopropiophenone metabolites of safrole (see Fig. 4), dependent upon whether the model substrate benzylamine, serotonin or tyramine was employed. The authors [13] concluded, "In correlating psychoactive properties of the allyl benzenes found in nutmeg and other essential oils, it is very probable that an additive psychoactive effect is caused by the numerous tertiary amino propiophenones formed from safrole, myristicin, elemicin and eugenol." Basically, it was being suggested that the psychoactive effects of allylbenzene-containing essential oils might be due to an indirect pharmacological effect, perhaps involving potentiation of serotonin levels in the brain. A solution to this conundrum was still not in sight. Then, it would appear that Oswald and his co-workers simply dropped these lines of enquiry after one final paper on the mechanism of formation of the tertiary aminopropiophenone metabolites [14].

Around this same time, two pharmacologists in Bonn were also pursuing the Shulgin hypothesis of "essential amphetamines" and they reported [15] that in an isolated rat liver perfused for 5 h, myristicin could be converted to 3-methoxy--4,5-methylenedioxyamphetamine (MMDA), by presumed metabolic addition of ammonia. MMDA is, of course, the *N*-demethyl derivative and metabolite of the recreational drug MDMA (Ecstasy). This single experiment, which relied on two-dimensional thin-layer chromatography, without support of mass-spectrometric data, was never reproduced.

A more recent study in rats and mice of a popular Brazilian folk medicinal plant, *Croton zehntneri*, from which a tea is made to treat "nervous disturbances", has been reported [16]. *Croton zehntneri* primarily contains methyleugenol and estragol [16]. Increasing oral doses of the essential oil from *Croton zehntneri* were administered orally and various pharmacological procedures carried out, including use of an open-field arena, pentobarbitone-induced hypnosis, stereotypic behaviour after apomorphine, haloperidol-induced catalepsy, amphetamine-induced hypermotility and pentylenetetrazole-induced convulsions. The oil was concluded to have CNS depressant effects, but from the results, a dopamine-related mechanism was eliminated. The reported findings were consistent with the

use of this plant in Brazilian folk medicine. However, it must be noted that all experiments were begun 60 min or later after the administration of the oil which, according to Oswald's findings (see above) would be outside the time window for a CNS stimulatory effect.

It would appear that reliable and reproducible evidence has been produced that a wide variety of naturally-occurring allylbenzenes are converted in the laboratory animals into so-called tertiary aminopropiophenones of variable chemical stability. The endogenous secondary amines that participate in these metabolic pathways are dimethylamine, piperidine and pyrrolidine (see Fig. 4). No *in vitro* counterpart of these *in vivo* reactions has ever been published and no enzyme system identified that could catalyze these somewhat bizarre reactions. While Shulgin's propositions [2–6] have not been confirmed *in toto*, there is some limited evidence that these nitrogen-containing metabolites of allylbenzenes may act as MAO inhibitors, which is a possible explanation for the hallucinogenic properties of nutmeg and other spices. Until recently, the proposition that spice constituents may be converted *in vivo* to psychotropic amphetamine derivatives is still kept alive in the scientific literature [17]. However, more recent metabolic studies, for example with myristicin in the rat *in vivo* and *in vitro*, failed to confirm the presence of nitrogenous metabolites [18]. However, the experimental conditions used by these authors would almost certainly lead to decomposition of these metabolites, as previously reported [9]. Nevertheless, new mechanisms for how allylbenzenes may interfere with CNS neurophysiology continue to be advanced, for example, that these compounds, by participating in transamination reactions (see Fig. 3), may interfere with the production of neurotransmitters [19]. What is clear is that this 40 year-old story has yet to reach its final conclusion.

Allylbenzenes as "essential amphetamines" – the *in furno* evidence

Central to the theme of this review is the idea that we consume spices such as clove, nutmeg and cinnamon only in the dark times of winter and not on hot summer days when they might appear inappropriate. Is this merely a tradition of Northern European cultures or might it have some pharmacological basis. The evidence has been reviewed that such spices contain alkenylbenzene derivatives, including the highly aromatic allylbenzenes, such as myristicin, elemicin and eugenol, and that these substances might be converted in the body to psychoactive metabolites akin to stimulants such as amphetamines. The evidence is at best equivocal. Nevertheless, there exists an alternative means by which consumption of certain foodstuffs may lead to amphetamine exposures, and that is the formation of these compounds during the cooking process, what I have called "*in furno*." Examination of the *Lebkuchen* recipe in Table 3 reveals chemical constituents that, when heated together *in furno* might plausibly result in some ammonia addition to the alkenylbenzene double bonds, which would lead to the presence in the *Lebkuchen* of 4-methoxyamphetamine (PMA) from (*E*)-anethole

and 4-hydroxy-3-methoxyamphetamine (HMA) from eugenol. It is readily calculated from Table 3 that just a 1% yield in these reactions could lead to amphetamine content in excess of 80 mg per kg *Lebkuchen*. Unfortunately, no scientific data on the content of these compounds in baked goods has ever been published to my knowledge. The formal hallucinogenic doses of PMA and is 50-80 mg [6] and for HMA is not known [6]. It may be sufficient for a person to ingest tiny amounts of these compounds from the winter diet, in order to elevate the mood and to help providing some added Christmas cheer. Until the appropriate laboratory and clinical investigations are performed, it is merely a subject of speculation and fantasy.

Non-amphetamine considerations

One is bound to ask if the alkenylbenzenes, or any of the other fragrant constituents of these winter spices, possess biological activity *per se*. We may start by asking why plants such as *Myristica frangrans* make such a large metabolic investment to synthesize a range of, not only alkenylbenzenes, but also terpenes and other odorous chemicals. It would appear that plants may not only produce these compounds to deter herbivores, such as caterpillars, but also may release them in response to herbivore damage to attract the herbivores' natural enemies, such as parasitic wasps [20]. Also of interest is the report that male Mediterranean fruit flies, when exposed to ginger root oil, have an increased mating success [21]. Are their similar effects reported in higher animals? Tajuddin *et al*. [22] have reported that ethanolic extracts of both nutmeg and clove stimulated mounting behaviour of male mice and improved mating performance. Treated male mice mounted 3–5 times more frequently than untreated controls in the first hour and 3–7 times more frequently in the third hour. The authors attributed this effect to "nervous stimulating activity", reminiscent of the reports of Oswald and colleagues [7–14]. The observed effect in the third hour was comparable to that of male mice

Table 3 – Typical recipe for Lebkuchen*

Ingredient	Relative amount (%)	Alkenylbenzene content
Honey	208 g (23.7)	–
Sugar	96 g (10.9)	–
Water	32 g (3.7)	–
Bread flour	480 g (54.8)	–
Ground ginger	2 g (0.2)	–
Ground cloves	2 g (0.2)	31.40 mmol eugenol
Ground cinnamon	3 g (0.3)	1.46 mmol eugenol
Ground anise seeds	1 g (0.1)	3.36 mmol (*E*)-anethole
Bakers ammonia (Triebsalz)	8 g (0.9)	84.40 mmol $(NH_4)_2CO_3$
Potash	4 g (0.5)	29.00 mmol K_2CO_3
Milk	40 g (4.6)	–
Total	**876 g (100)**	

*Adapted from www.pastrywiz.com/cookies/lebkuche.htm

treated with sildenafil (Viagra) [22]. These same authors reported that a clove extract displayed marked dose-dependent aphrodisiac properties in male rats [23]. Clove is the principal source of alkenylbenzenes, such as eugenol, in the typical *Lebkuchen* recipe (Table 3). This possibly furnishes another explanation of the role of the "nervous stimulating activity" attributable to winter spices, and one which may have a Darwinistic selective advantage. I will confess to a personal interest here, having been born in September and presumably conceived close to mid-winter.

Perhaps, like aromatherapy, there is something about the odours of these winter spices that medical science has yet to reveal. After all, smell is the one sense that stimulates the memory, returning to us pleasurable thoughts of past experiences. In *A Natural History of the Senses*, Diane Ackerman writes,

> *"Nothing is more memorable than smell. One scent can be unexpected, momentary, and fleeting, yet conjure up a childhood summer beside a lake…"*

Maybe we simply need those kitchen odours at Christmas time to refresh ourselves of the feelings of good cheer. It may have nothing to do with pharmacology, simply the lifting of our spirits by the best memories of childhood winters that we have stored forever away, available for downloading once triggered by a particular odour or combination of smells. One thing is, however, certain. The imprint of far-off and exotic places is reborn in us each dark and cold European winter through the medium of clove and ginger, nutmeg and cinnamon. Whether there is also a definable pharmacological component to this experience remains to be elucidated.

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References

1. SHULGIN A. T., BUNNELL S., SARGENT T. III.: The psychotomimetic properties of 3,4,5-trimethoxyamphetamine. *Nature* 189: 1011–1012, 1961.
2. SHULGIN A. T.: Concerning the pharmacology of nutmeg. *Mind* 1: 299–302, 1963.
3. SHULGIN A. T.: 3-Methoxy-4,5-methylenedioxy amphetamine, a new psychotomimetic agent. *Nature* 201: 1120–1121, 1964.
4. SHULGIN A. T.: Possible implication of myristicin as a psychotropic substance. *Nature* 210: 380–384, 1966.
5. SHULGIN A. T., SARGENT T., NARANJO C.: The chemistry and psychopharmacology of nutmeg and of several related phenylisopropylamines. In: *Ethnopharmacologic Search for Psychoactive Drugs*. EFRON D. H., HOLMSTEDT B., KLINE N. S. (EDS.), Public Health Service Publication No. 1645, Washington DC, 1967, 202–214.

6. SHULGIN A., SHULGIN A.: *PIHKAL. A Chemical Love Story*, Transform Press, Berkeley, 2000, 860.
7. OSWALD E. O., FISHBEIN L., CORBETT B. J.: Metabolism of naturally occurring propenylbenzene derivatives. I. Chromatographic separation of ninhydrin-positive materials of rat urine. *J. Chromatogr.* 45: 437–445, 1969.
8. OSWALD E. O., FISHBEIN L., CORBETT B. J., WALKER M. P.: Metabolism of naturally occurring propenylbenzene derivatives. II. Separation and identification of tertiary aminopropiophenones by combined gas-liquid chromatography and chemical ionization mass spectrometry. *J. Chromatogr.* 73: 43–57, 1972.
9. OSWALD E. O., FISHBEIN L., CORBETT B. J., WALKER M. P.: Urinary excretion of tertiary amino methoxy methylenedioxy propiophenones as metabolites of myristicin in the rat and guinea pig. *Biochim. Biophys. Acta* 244: 322–328, 1971.
10. OSWALD E. O., FISHBEIN L., CORBETT B. J., WALKER M. P.: Chemical lability of the tertiary aminopropiophenones of eugenol as characterized by combined gas-liquid chromatography and chemical ionization mass spectrometry. *J. Chromatogr.* 73: 59–72, 1972.
11. OSWALD E. O., FISHBEIN L., CORBETT B. J., WALKER M. P.: Identification of tertiary aminomethylenedioxypropiophenones as urinary metabolites of safrole in the rat and guinea pig. *Biochim. Biophys. Acta* 230: 237–247, 1971.
12. MCKINNEY J. D., OSWALD E. O., FISHBEIN L., WALKER M. P.: On the mechanism of formation of Mannich bases as safrole metabolites. *Bull. Environ. Contam. Toxicol.* 7: 305–310, 1972.
13. BANGDIWALA V. S., OSWALD E. O.: Metabolic interaction of secondary amines and tertiary amino propiophenones with monoamine oxidase systems. *Chem-Biol. Interact.* 14: 141–148, 1976.
14. PEELE J. D. JR., OSWALD E. O.: Metabolism of naturally occurring propenylbenzene derivatives. III. Allylbenzene, propenyl benzene, and related metabolic products. *Biochim. Biophys. Acta* 497: 598–607, 1977.
15. BRAUN U., KALBHEN D. A.: Nachweis der Bildung psychotroper Amphetamin-Derivate aus Inhaltsstoffen der Mustkatnuß. *Dtsch. Med. Wschr.* 97: 1614–1615, 1972.
16. BATATINHA M. J. M., DE SOUZA-SPINOSA H., BERNARDI M. M.: *Croton zehntneri*: possible central nervous system effects of the essential oil in rodents. *J. Ethnopharmacol.* 45: 53–57, 1995.
17. EHRLERS D., KIRCHHOFF J., GERARD D., QUIRIN K.-W.: High-performance liquid chromatography analysis of nutmeg and mace oils produced by supercritical CO_2 extraction – comparison with steam-distilled oils – comparison of East Indian, West Indian and Papuan oils. *Int. J. Fd. Sci. Technol.* 33: 215–223, 1998.
18. LEE H. S., JEONG T. C., KIM J. H.: In vitro and in vivo metabolism of myristicin in the rat. *J. Chromatogr. B.* 705: 367–372, 1998.
19. SANGALLI B. C., CHIANG W.: Toxicity of nutmeg abuse. *Clin. Toxicol.* 38: 671–678, 2000.
20. TURLINGS J. C. J., TUMLINSON T. H., LEWIS W. J.: Exploitation of herbivore-induced plant odors by host-seeking parasitic wasps. *Science* 250: 1251–1253, 1990.
21. SHELLY T. E., MCINNES D. O., PAHIO E., EDU J.: Aromatherapy in the Mediterranean fruit fly (*Diptera*: *Tephritidae*): sterile males exposed to ginger root oil in prerelease storage boxes display increased mating competitiveness in field-cage trials. *J. Econ. Entomol.* 97: 846–853, 2004.
22. TAJUDDIN, AHMAD S., LATIF A., QASMI I. A.: Aphrodisiac activity of 50% ethanolic extracts of *Myristica fragrans* Houtt. (nutmeg) and *Syzygium aromaticum* (L) Merr. & Perry. (clove) in male mice: a comparative study. *BMC Complement. Altern. Med.* 3: 6–10, 2003.
23. TAJUDDIN, AHMAD S., LATIF A., QASMI I. A.: Effect of 50% ethanolic extract of *Syzygium aromaticum* (L) Merr. & Perry. (clove) on sexual behaviour of normal male rats. *BMC Complement. Altern. Med.* 4: 17–23, 2004.