Volume 53(2):77-82, 2009
Acta Biologica Szegediensis
http://www.sci.u-szeged.hu/ABS

REVIEW

Camphor: benefits and risks of a widely used natural product

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ABSTRACT The main aspects of the non-clinical profile of D-camphor, a natural product widely used as a common remedy for several symptoms, are reviewed. The pharmacodynamics and toxicity of this substance are analyzed, with regard to all the literature available, in order to assess a risk profile and better understand the positive and negative results connected with its use. The general conclusion is that the main risks of camphor as a medicinal product are mainly due to a somehow diffused attitude of considering it as "not a real medicine", and to its consequent sometimes not sufficiently careful administration.

Acta Biol Szeged 53(2):77-82 (2009)

KEY WORDS

D-camphor
pharmacodynamic
pharmacokinetics
risk/benefit assessment
toxicity

Camphor (Figure 1) is a natural product deriving from the wood of the camphor laurel (*Cinnamomum camphora* L.) trees through steam distillation and purification by sublimination; the trees used should be at least 50 years old. It also occurs in some other related trees in the laurel family, notably *Ocotea usambarensis* Eng., and can also be obtained from the plant *Lippia dulcis* Trev., but this is not a major industrial source (Compadre et al. 1986). A major source of camphor in Asia is *Ocimum kilimandscharicum* Baker ex Gurke.

Camphor can also be produced synthetically from vinyl chloride and cyclopentadiene, passing through the intermediate dehydronorbornyl chloride. The naturally occurring form is dextrorotatory and the synthetic form optically inactive (Budavari 1989; Reynolds 1989).

Camphor has a counterirritant, rubefacient and mild analgesic action, and is a major component of liniments for relief of fibrositis, neuralgia and similar conditions. It can be used as a mild expectorant; if ingested, camphor has irritant and carminative properties. Camphorated-oil, a solution in oil given through intramuscular or subcutaneous way, can be used as a circulatory and respiratory stimulant, but this use is considered hazardous. When, in combination with menthol and chenodeoxycholic acid, it has been used to aid dispersal of bile duct stones, although this is no longer recommended (Reynolds 1989).

Aim of the present work is to provide an overview over pharmacological and toxicological aspects of camphor, in order to assess its safety profile and evaluate the level of risk connected with its use.

Accepted Oct 20, 2009
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Pharmacology

Pharmacodynamics

Camphor, a natural product derived from the wood of the tree *Cinnamomum camphora*, has a long history of use as antiseptic, analgesic, antipruritic, counterirritant and rubefacient (Hercogová 2005; Lynde et al. 2008). Its success and wide medical use, especially in topical preparations, is connected to its mild local anesthesizing effect and to the production of a circumscribed sensation of heat, together with its characteristic and penetrating odour that is by most of people associated to the idea of a strong and effective medicine (Gibson et al. 1989).

Camphor is today mostly used in the form of inhalants and of camphorated oil, a preparation of 19% or 20% camphor in a carrier oil, for the home treatment of colds (Jochen and Theis 1995) and as a major active ingredient of liniments and balms used as topical analgesics (Xu et al. 2005).

The antitussive, nasal decongestant and expectorant action of camphor and of its derivatives was one of the first ones to be systematically investigated (Inoue and Takeuchi 1969).

Its nasal decongesting activity seems to be not purely mechanic, but connected with the stimulation of cold receptors in the nose. The inhalation of camphor vapours (so as the one of eucalyptus and menthol vapours) on a sample of volunteers increased the nasal sensation of airflow through the induction of cold sensation in the nose, despite of actually not affecting nasal resistance to airflow (Burrow et al. 1983).

More recent studies pointed out how camphor efficacy in the treatment of cold is due to its antispasmodic action (Astudillo et al. 2004), and how the effects of camphor on bronchospasm are connected to its anti-histaminergic and anti-cholinergic activities (Görnemann et al. 2008). In fact,

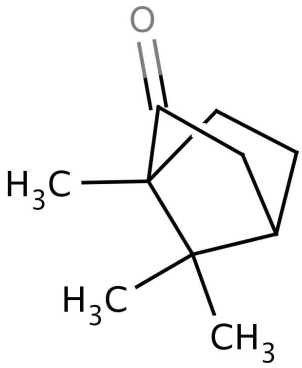

Figure 1. Structural formula of Camphor, a bicyclic monoterpene ketone (1,7,7-trimethylbicyclo [2.2.1] heptan).

camphor appears to be effective to reduce histamine H1 and muscarinic M3 receptor-mediated bronchocostriction (Görnemann et al. 2008), and this action relates also to the inhibition of cough (Kreutner et al. 2000).

Camphor was administered in the form of aromatic vapor, at the concentrations of 50, 133 and 500 μg l^{-1}, to guinea pigs subject to chemically induced cough. No effect were registered at the lowest concentrations, but 500 μg l^{-1} camphor gave a 33% reduction of cough frequency, to which an increase in cough latency coincided (Laude et al. 1994).

The analgesic proprieties of camphor are largely known and applied, but little is known about the molecular mechanisms that are at their basis. (Xu et al. 2005).

Moqrich et al. (2005) demonstrated that camphor activates TRPV3, a member of transient receptor channel superfamily, leading to excitation and desensitization of sensory nerves. The notorious effect of generation of a sensation of heath associated with topic application of camphor (Green 1990) is a consequence of this activation. In fact, TRPV3 is a warm-sensitive Ca^{2+}-permeable cation channel, that once activated originates the warm sensation, actually simulating an effective increase of temperature in the treated area (Xu et al. 2006). This effect, caused by an increase in intracellular Ca^{2+} levels, is typical also of other natural compounds as carvacrol, eugenol and thymol (Xu et al. 2006).

Anyway excessive and repeated application of camphor can lead to sensibilization of TRPV3, in apparent contrast with its analgesic role (Peier et al. 2002; Moqrich et al. 2005).

The antipruritic and counterirritant activity of camphor is instead associated with its capacity of activating TRPV1 - another member of TRP channel superfamily - at the level of dorsal root gangliar [DRG] neurons and inhibiting TRPA1 channels (Moqrich et al. 2005; Nagata et al. 2005), action that is in common with other TRPV1 agonists (Bhave et al. 2002; Xu et al. 2006; Belmonte and Viana 2008). The recently clarified activity of camphor as a TRPA1 inhibitor has been utilized by Lee et al. (2008) for pretreatment of human embryonic kidney cells tested for membrane potential changes elicited by thymol, showing how the response to thymol is blocked by camphor. Bang et al. (2007) showed camphor to suppress acute pain in mouse consequent to intradermal administration of acetaldehyde into mouse footpads.

Capsaicin shares the same action with camphor, but performs it more slowly and less completely; on the other side camphor efficacy is lower, since higher concentrations are required (Xu et al. 2005). Studies on rats demonstrated that the actions of capsaicin and camphor are segregated (Wu et al. 2005), *i.e.* they are mediated by distinct channel regions, and camphor did not activate TRPV1 in capsaicin-insensitive chickens (Xu et al. 2005; Jordt and Julius 2002).

Camphor also inhibits other related TRP channels such as ankyrin-repeat TRP1 (TRPA1), which is a further evidence underlying its analgesic effects (Xu et al. 2005).

Camphor was shown to inhibit mitochondrial respiration. Administration of up to 8 μM of camphor inhibited respiration rate in rat-liver mitochondria, nearly halving the oxygen consumption; this suggests that camphor may be used in oxygenating tumors prior to radiotherapy (Guilland-Cumming and Smith 1979; 1982).

Camphor can also be a potential radiosensitizing agent in radiotherapy. Treatment with camphor (0.5 μmol · body wt^{-1}) 45 minutes before local x-irradiation at the dose levels of 30, 80, 100 or 120 Gy was performed on male C3H/Jax mice bearing transplanted mammary tumours. Sequential measurement of the tumour volumes during 45 days after the irradiation revealed a 4.8 delay of the maximum enhancement ratios in tumour growth (Goel and Roa 1988).

D-camphor (1100 μg ml^{-1}) inhibited oxidative metabolism in *E.coli* (Cardullo and Gilroy 1975). Succinic, lactic and NADH-oxidase activities were inhibited, while NADH and succinic DCPIP oxidoreductase enzymes were unaffected. The restoration of succinic oxidase activity by ubiquinone (Q6) but not by vitamin K1 indicates that D-camphor may operate this inhibition by affecting quinone functions.

Pharmacokinetics

Camphor is readily absorbed from all the sites of administration, after inhalation, ingestion or dermal exposure (Baselt and Cravey 1990). Peak plasma levels were reached by 3 hours post-ingestion when 200 mg camphor was taken alone, and 1 hour post-ingestion when it was ingested with a solvent (Tween 80; Koppel et al. 1988).

In case of dermal application, the volume of the absorption is relatively low in comparison with the speed of the process. After application of different numbers of commercial patches [2, 4 or 8] to the skin of human subjects during 8 hours, the levels of camphor in the plasma were assayed with selective gas-cromatography (Valdez et al. 1999; Martin et

al. 2004). Maximum camphor plasma concentration resulted in a range between 35.2 and 46.8 ng/ml^{-1} in the case of 8 patches, between 19.6 and 34 ng/ml^{-1} for the 4 patches while almost undetectable concentrations were observed when only 2 patches had been applied, showing that dermal absorption is prompt but not massive.

Camphor is distributed throughout the whole body, and can permeate the placenta; for this reason it must be recommended that the use of this product is avoided during pregnancy and lactation (Sweetman 2005).

Its volume of distribution is 2-4 L/kg (Koppel et al. 1988); plasma protein binding has been estimated as 61% (Koppel et al. 1982).

After its absorption and distribution, camphor undergoes hepatic metabolism: it is hydroxylated in the liver into hydroxycamphor metabolites (Sweetman 2005).

Asahina and Ishidate (1933; 1934; 1935) isolated *cis*- and *trans*- -hydroxycamphor and camphor- -carboxylic acid from the urine of dogs that had been fed with camphor; Shimamoto (1934) obtained 3-hydroxycamphor (15%), 5-hydroxycamphor (55%) and trans- -hydroxycamphor (20%) from the urine of dogs, and 5-hydroxycamphor [as major metabolite] and 3-hydroxycamphor from the urine of rabbits.

Robertson and Hussain (1969) observed that (+)-camphor and (-)-camphor increase the content of glucuronide in the urine of rabbits; (+)-camphor was moreover reduced to (+)-borneol as well as being hydroxylated to (+)-5-endo-hydroxycamphor [major product] and (+)-3-endo-hydroxycamphor.

Hydroxylation of camphor, as well as norcamphor, pericyclocamphanone and 5,5-difluorocamphor, is mainly performed by cytochrome P450 (Collins and Loew 1988), a class of heme-containing monooxygenases that are distributed in the whole body (Boxenbaum 1984), by hydrogen abstraction (Wand and Thompson 1986). Cytochrome P450 is responsible for camphor conversion into 5-hydroxycamphor (Gelb et al. 1982), while 3-hydroxycamphor is the primary product of non-enzymatic hydroxylation of camphor (Land and Swallow 1979). Camphor hydroxylation by cytochrome P450 occurs with a different region-specificity for camphor and its related compounds (Collins and Loew 1988).

Hydroxylated metabolites are then conjugated with glucuronic acid and excreted in the urine (Sweetman 2005). The half-life of 200 mg of camphor was 167 minutes when ingested alone, and 93 minutes when ingested with a solvent (Tween 80) (Koppel et al. 1988).

Camphor can modulate the activities of hepatic enzymes involved in phase I and phase II drug metabolism. 50, 150 and 300 mg/Kg^{-1} of camphor dissolved in 0.1 ml of olive oil was administered daily to female Swiss Albino mice during 20 days. At its highest concentration it caused a significant increase in the activities of cytochrome P450, cytochrome b5, aryl-hydrocarbon hydroxylase and glutathione S-transferase, significantly elevating the level of reduced glutathione in the liver (Banerjee et al. 1995).

Interactions

Very few studies of pharmacological interactions between camphor and other compounds are present in literature. In a study combining the administration of D-camphor and an extract from fresh crataegus berries, a synergic action of the two preparations emerged in ameliorating cardiac performances. Both D-camphor and the extract contributed in an increase in total peripheral resistance induced by an increase tone of the arterioles, and while the former appeared to be the main factor in inducing the rapid initial effect, the former added a long-lasting effect (Belz and Loew 2003).

Toxicity

Camphor occurs in nature in its dextrorotatory form (D-camphor), while the laevorotatory form (L-camphor) exists only as a synthetic form. The two enantiomers present different profiles of toxicity.

D-camphor, L-camphor and their racemic mixture were tested for toxicity in mice. At 100 mg · Kg b.w.$^{-1}$ the natural form was non toxic, while the synthetic form induced different kinds of toxic and behavioural effects such as body jerks and hunched posture; the racemic mixture showed similar effects to the L-form (Chatterjie and Alexander 1986).

The oral administration of acute doses of D-camphor to rats and rabbits caused pronounced signs of toxicity. In rats, the consume of food was reduced proportionally to the administered dose, starting from 464 mg · Kg b.w.$^{-1}$ · day^{-1}, and at 1000 mg · Kg b.w.$^{-1}$ · day^{-1} convulsions and pilo-erection were observed, connected with a reduction of motility and weight gain. Reduced body weight gain and food consumption were observed in rabbits treated with 681 mg · Kg b.w.$^{-1}$ · day^{-1} (Leuschner 1997).

Camphor showed porphyrogenic activity in primary cultures of chick embryo - liver cells, with enhanced porphyrin accumulation ranging from 5- to 20-fold (Bonkovsky et al. 1992).

The main problems about camphor toxicity in humans are connected more to the large availability of camphor-containing products and their diffused perception as unhazardous medicines rather than in the intrinsic toxicity of camphor. The daily maximum human therapeutic dose is in fact approximately 1.43 mg · Kg^{-1}, which corresponds to a therapeutic ratio of more than 450 for the endpoint toxicity, reflecting a wide margin of safety (Leuschner 1997). On the other side, as mentioned above, camphor is present in several over-the-counter products, its use as a familiar remedy is commonly accepted, but still some lack of information persists among the consumers.

Cases of camphor intoxication in humans, especially children, are relatively frequent, mostly because of accidental ingestion (Siegel and Wason 1986). More than 100000 cases of ingestion exposures to camphor-containing products were registered between 1990 and 2003 (Manoguerra et al. 2006), causing a range of symptoms that comprises convulsion, lethargy, ataxia, severe nausea, vomiting and coma (Koppel et al. 1988; Manoguerra et al. 2006).

Reproduction toxicity

D-camphor was orally administered to pregnant rats and rabbits during the period of organogenesis to test its embryotoxicity. Doses up to 1000 mg · Kg b.w.$^{-1}$ · day^{-1} to rats and up to 681 mg · Kg b.w.$^{-1}$ · day^{-1} to rabbits showed no teratogenic effects, and in none of the animals were observed higher rates of mutations or malformations (Leuschner 1997).

Mutagenicity and cancerogenicity

In a Salmonella/microsome assay, the upper limit of the dose interval tested for (+/-) camphor resulted to be the highest non-toxic dose, suggesting that the compound is not mutagenic in the Ames test (Gomes-Carneiro et al. 1998).

A single dose of camphor (0.5 μM · g^{-1}) administered 30, 45 or 60 minutes before gamma irradiation significantly reduced the frequency of sister-chromatid exchanges in mouse bone marrow, showing therefore a radiomodifying influence (Goel at al. 1989).

Discussion and Conclusions

Camphor is familiar to many people as a principal ingredient in topical home remedies for a wide range of symptoms, and its use is well consolidated among the population of the whole world, having a long tradition of use as antiseptic, antipruritic, rubefacient, abortifacient, aphrodisiac, contraceptive and lactation suppressant.

In particular, the analgesic and antipruritic action of the compound make it appreciated by a large number of consumers, by whom it is used in the form of essential oil for cutaneous application. Itch is a complex phenomenon, being difficult to localize and quantify (Wahlgren 1995) and involving a variety of skin surface receptors, peripheral and central nerves and specific brain regions. The treatment of itch usually relies on antisthamines, corticoids or various topical remedies (Langner and Maibach 2009) among which camphor has a prominent role. The analgesic action is due to its interacions with members of TRP channel superfamily

Camphor is therefore an important remedy for symptomatic treatment of itching, especially in patients affected by contact dermatitis, because it goes to affect directly the cutaneous nerve ending, as other agents like pramoxine, phenol and menthol do (Burkhart and Burkhart 2003).

Camphor has also an important role in the treatment of cough and colds thanks to its antispasmodic activity, due to anti-histaminergic and anti-cholinergic action that causes depression of bronchospasm coupled with inhibition of cough.

This compound has also a long history of scientific studies on its action and on the way through which it is metabolized in the organisms of both humans and animals, due to the general interest that it has always arisen among common people and scientists. Already in 1879, Schmeideberg and Meyer were analyzing the metabolites isolated from the urine of dogs that had been fed with (+/-) camphor (Schmiedeberg and Meyer 1879), and during the first half of the twentieth century the number of studies focused on its pharmacology and pharmacokinetics has been remarkable.

The bibliographic search that was performed for the compilation of this toxico-pharmacological overview revealed a rich literature existing on camphor, and put in evidence the large amount of works focused on toxic aspects of camphor that were published during the last 30 years; a great number of reports concerning cases of camphor intoxication were also collected. In most cases camphor intoxication occurred following accidental ingestion of camphor-containing product, and sometimes lethal episodes of intoxication of infants due to application of camphor to their nostrils were collected.

As it emerges from all the observed data the toxic risks of camphor-containing products in general, and of camphorated oil in particular, are connected essentially with its improper uses, *e.g.* accidental ingestion, but camphor does not represent a threaten for safety when used on the target patients, following the indicated dosages and the contraindications. Special care must be taken during pregnancy, due to the fact that camphor crosses the placental barrier, and camphor and camphor containing products should be avoided in children who have a history of febrile convulsions or other predisposing factors for convulsions (Galland et al. 1992).

In the past, when camphor was used medicinally, the oral doses ranged from 120-300 mg (Wade 1977), and the parenteral dose range was from 60-200 mg (not recommended anymore).

Camphorated oil can be used with no risks for safety when following the prescriptions. The relatively diffused tendency to the improper use of camphor (high dosages, accidental ingestion, use on infants) is connected with the perception of the product, by many consumers, as a sort of "panacea" with no contraindication. More and more accessible information is therefore necessary to bring to a "responsabilization" of the consume of this product, in order to avoid hazardous situations.

All the above considerations allow the conclusion that camphor in its form of camphorated oil can be safely used at the proposed dosages, on the indicated patients target, for topic application.

Acknowledgements

The Authors would like to thank Annie Hart (A.R.S.) and Marina Ribatski (B.D.R.) for useful help during the elaboration of the manuscript.

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