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# Biological Activity Prediction of an Ethno Medicinal Plant *Cinnamomum camphora* Through Bio-informatics

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## Introduction

The camphor tree (*Cinnamomum camphora*) is a broad-leaved, evergreen tree. The alternate leaves are shiny dark green above and lighter green below and have wavy margins with three distinct yellow veins. A distinctive odor of camphor is emitted when the leaves are crushed. The flowers are inconspicuous and the fruit is a black pea-sized berry. The camphor tree grows in full sun or partial shade and it is drought tolerant but not particularly cold tolerant. It invades hardwood forests, upland pine and scrub woods, fence rows and urban green spaces.

The traditional oils are obtained from the wood and bark of this plant (Stahl, 1957; Pandey et al., 1997). The oil, with a high content of camphor, has an important antifungal activity ( Sattar et al., 1991). *C. camphora* has several chemical varieties which have different essential oil compositions (Moellenbeck et al., 1997). Two varieties have been exploited commercially, *C. camphora* Nees & Eberm., the most valuable for the presence of camphor, and (*C. camphora* Nees & Eberm var. *linaloolifera*) for its high content of linalool. These varieties are morphologically similar, but they show different essential oil compositions and for this reason are considered physiological varieties (Guenther, 1950). The oils obtained from the leaves by steam distillation have economic importance as their main components are camphor and linalool.

The pahrmacognosy of the phytols in the *C. camphora* are given below:

**Cinnamon bark** oil possesses the delicate aroma of the spice and a sweet and pungent taste. Its major constituent is cinnamaldehyde, but other, minor components impart the characteristic odour and flavour. It is employed mainly in the flavouring industry where it is used in meat and fast food seasonings, sauces and pickles, baked goods, confectionery, cola-type drinks, tobaccoflavours and in dental and pharmaceutical preparations. Perfumery applications are far fewer than in flavours because the oil has some skin-sensitizing properties, but it has limited use in some perfumes.

**Cinnamon leaf** oil has a warm, spicy, but rather harsh odour, lacking the rich body of the bark oil. Its major constituent is eugenol rather than cinnamaldehyde. It is used as a flavouring agent for

seasonings and savory snacks. As a cheap fragrance, it is added to soaps and insecticides. The oil's high eugenol content also makes it valuable as a source of this chemical for subsequent conversion into iso-eugenol, another flavouring agent.

**Cassia oil** is distilled from a mixture of leaves, twigs and fragments of bark. Cinnamaldehyde is the major constituent and it is used mainly for flavouring cola-type drinks, with smaller amounts used in bakery products, sauces, confectionery and liqueurs. Like cinnamon bark oil, its use as a fragrance is limited by its skin sensitizing properties. (FAO)

An FAO listing of the cinnamomum species that yield the chemical isolates which are of therapeutic, medicinal and economic importance is given below:

***Cinnamomum* species with actual or potential use as sources of chemical isolates** (FAO).

| **Species** | **Major oil constituent** |
|---|---|
| *C. camphora* | Camphor, linalool, safrole and cineole |
| *C.camphora var.linaloolifera* | Linalool |
| *C. sulphuratum* | Linalool |
| *C. petrophilum* | Safrole |
| *C. mollissimum* | Safrole |
| *C. mollissimum* | Benzyl benzoate |
| *C. pubescens* | Eugenol |
| *C. tamala* | Cinnamaldehyde or eugenol |

Camphor has a long history of herbal use. It has been used internally in the treatment of hysteria, but in modern day herbalism it is mainly used as an essential oil and internal use is not advised [1]. The wood and leaves are analgesic, antispasmodic, odontalgic, rubefacient, and are also used as a stimulant. An infusion is used as an inhalant in the treatment of colds and diseases of the lungs [2, 3, 4]. The essential oil, which can be obtained by distillation of the chipped branches, trunk and wood of the tree, or from the leaves and twigs, is the most suitable form of usage. Wood 24 - 40 years old is normally used [5]. The essential oil is anthelmintic, antirheumatic, antispasmodic, cardiotonic, carminative, diaphoretic, sedative and tonic [6, 7, 8, 9]. It is used externally in liniments for treating joint and muscle pains, balms for chilblains, chapped lips, cold sores, skin diseases, etc., and as an inhalant for bronchial congestion [8]. Some caution is advised, excessive use causes vomiting, palpitations, convulsions and death [8]. It is possible that the oil can be absorbed through the skin, causing systemic poisoning [8]. The essential oil is used in aromatherapy. Its keyword is 'Piercing' [9]. It is used in the treatment of digestive complaints and depression [8].

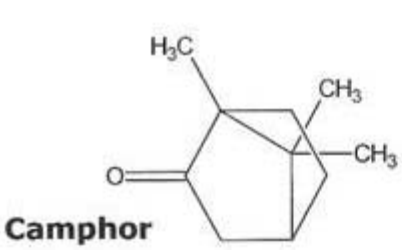
Sassafras oils from *Cinnamomum camphora* and *Ocotea pretiosa*, respectively, are both sources

of safrole, which is used to manufacture heliotropin, a valuable flavour and fragrance compound. *C. camphora* is also a source of natural camphor (FAO).

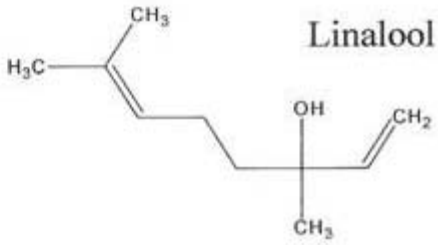
Rosewood oil was once an important source of linalool, an aroma chemical in its own right but also a precursor for other fragrance compounds. Although cheaper sources of linalool are now utilized (still of plant origin), *Cinnamomum* spp. are also proving its best to add it to the content (FAO).

Having established that there is a market for a particular chemical substance and an opportunity for new or improved production, the action is necessary to put these ideas into practice in the field of its activity prediction. Biological Activity Spectrum (BAS) of a compound represents the complex of pharmacological effects, physiological & biochemical mechanisms of action, specific toxicity (mutagenicity, carcinogenicity, teratogenicity & embryotoxicity) which can be revealed in a compound's interaction with the biological system. Biological Activity Spectrum describes the intrinsic properties of the compound dependent on it's structural particularities. It may be revealed in experiment under any conditions (dosage, route of administration, biological object, age, sex, etc.).

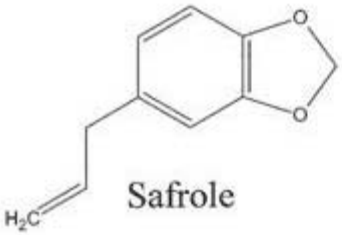
The objective of our work was to screen the five major phytols of *C. camphora* which are very much of medicinal importance. For our work, we have used computational techniques with the internet source as a backend.



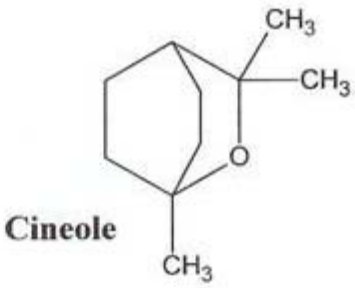
Camphor



Linalool



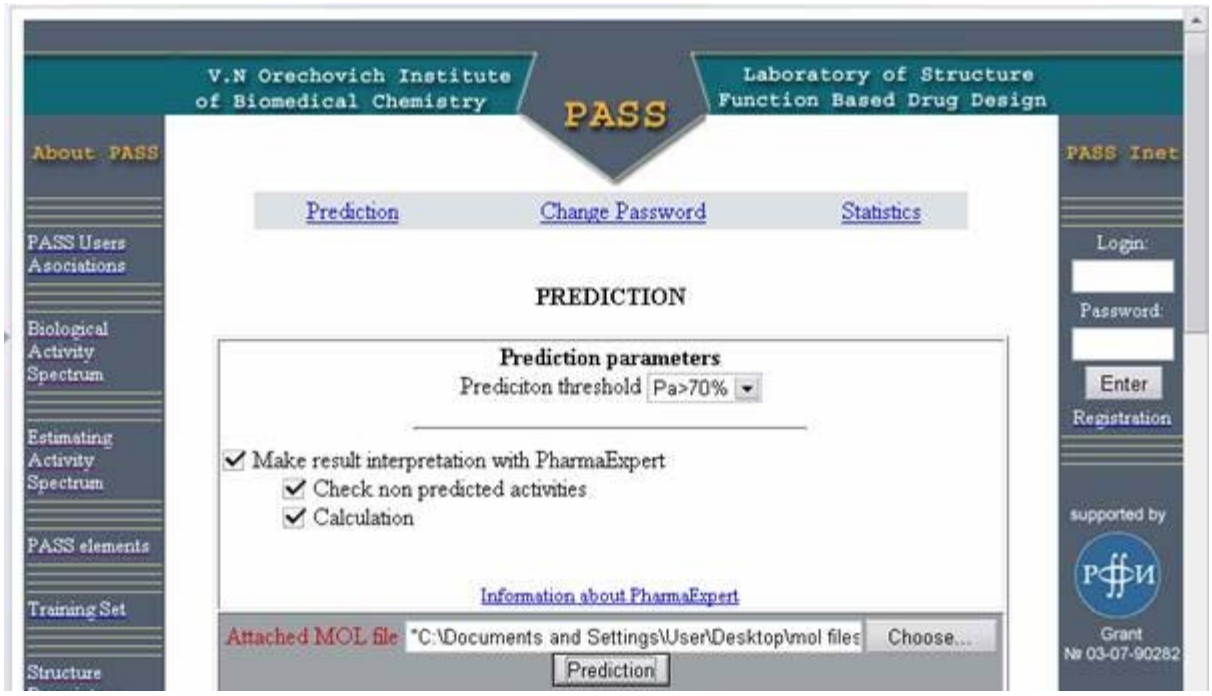
Safrole



Cineole

## Materials and Methods

The structures of the phytochemicals present in the *C. camphora* are (Camphor, linalool, safrole and cineole) are obtained from the pubchem compound repository. The structures are drawn using the Chem skech package 11.0 belonging to the ACD Chem laboratory. The biological activity spectrum was drawn using the acticvity prediction server PASS – Prediction of Activity Spectra of Substances.




Multilevel Neighborhoods of Atoms (MNA) structure descriptors of a molecule are generated on the basis of connection between (C) and of atoms types (A) presented in the compound. Connection table contains data on the valent bonds in a molecule. Various bond types are not specified (topological approximation). All hydrogens based on valencies and partial charges of atoms are taken into account. The structure of a molecule is represented as the set of multilevel neighborhoods of atom's descriptors calculated iteratively. Zero-level's descriptor is presented by the type of atom and special dash label if the atom is not included into the cycle. This process is extended from the $1^{st}$ level to the $2^{nd}$, $3^{rd}$, etc. neighborhoods of the atom.

Biological activity is the result of a chemical compound's interaction with a biological entity. In clinical study, a biological entity is represented by a human organism. In preclinical testing, it is the experimental animals (in vivo) and experimental models (in vitro). Biological activity depends on the peculiarities of a compound (structure and physico-chemical properties), biological entity (species, sex, age, etc.), mode of treatment (dose, route, etc.).

Any biologically active compound reveals a wide spectrum of different effects. Some of them are useful in the treatment of definite diseases, but the others cause various side and toxic effects. Total complex of activities caused by the compound in biological entities is called the "biological activity spectrum of the substance".

The algorithm used for the activity prediction is as follows:

**Algorithm Prediction:** (The source is obtained from the PASS description through its server in the training set).

The compound under prediction in structural descriptors are generated. For each activity the following values are calculated:

**uj = a i ArcSin{ri(2pij-1)}, u0j = a i ArcSin{ri(2pj-1)}**

**where,**
**n is the total amount of compounds in the training set;**
**ni is the amount of compounds, that have the descriptor i;**
**nj is the amount of compounds, that reveal the activity j;**
**nij is the amount of compounds, that have both the descriptor i and the activity j;**

**pj = a i nij/a i ni is the estimate of a priori probability of activity j;**
**pij = nij/ni is the estimate of the conditional probability of the activity j for the descriptor i;**
**m is the number of descriptors for the compound under prediction;**
**ri = ni/(ni + 7.7/m) is the regulating factor;**

**Prj is the initial estimate of the probability of the activity j for the compound under prediction;**
**CPj is the cutting point;**
**E1j(CPj) is the estimate of 1st kind error probability;**
**E2j(CPj) is the estimate of 2nd kind error probability;**

**The 1st kind error is observed when the compound under prediction actually is active but Prj < CPj;**
**The 2nd kind error is observed when the compound under prediction is considered as inactive but Prj > CPj;**

**LOO is the leave-one-out procedure:**

**for each compound in the training set the values n, ni, nj, nij are changed for n-1, ni-1, and nj-1, nij-1 when it has activity j, and the estimates Prj are calculated based on the other compounds in the training set.**

**MEP is the maximal error of prediction.**
**sj = Sin(uj/m), s0j = Sin(u0j/m)**

**Prj = (1+(sj-s0j)/(1-sjs0j))/2**

**Validation criterion:**

For each compound in the training set the LOO estimates of Prj are calculated.For each activity the estimates of **E1j(CPj)** and **E2j(CPj)** are calculated. The cutting points **CPj*** which provides equality

$$E1j(CPj^*) = E2j(CPj^*)$$

are calculated. The maximal error of prediction MEP is:

$$MEPj = E1j(CPj^*) = E2j(CPj^*)$$

## Results

**Camphor**

17 Possible activities at Pa > 70%

| Pa | Pi | Activity |
|---|---|---|
| 0,841 | 0,025 | Antidiabetic |
| 0,841 | 0,025 | Phosphatase inhibitor |
| 0,841 | 0,025 | Antineoplastic |
| 0,841 | 0,025 | Phosphatase inhibitor |
| 0,728 | 0,008 | Neuroprotector |
| 0,728 | 0,008 | Nerve growth factor agonist |
| 0,728 | 0,008 | Antiparkinsonian |
| 0,728 | 0,008 | Nerve growth factor agonist |
| 0,977 | 0,002 | Analeptic |
| 0,762 | 0,028 | Cardiovascular analeptic |
| 0,942 | 0,002 | Respiratory analeptic |
| 0,753 | 0,007 | Cognition disorders treatment |
| 0,753 | 0,007 | Alzheimer's disease treatment |
| 0,753 | 0,007 | Neurotrophic factor enhancer |
| 0,728 | 0,008 | Nerve growth factor agonist |
| 0,753 | 0,007 | Neurotrophic factor enhancer |
| 0,728 | 0,008 | Nerve growth factor agonist |
| 0,902 | 0,007 | Dermatologic |
| 0,739 | 0,008 | Antiacne |
| 0,739 | 0,008 | Antipruritic |
| 0,739 | 0,008 | Antieczematic atopic |
| 0,739 | 0,008 | Antipruritic |
| 0,902 | 0,012 | Antiseborrheic |
| 0,728 | 0,008 | Psychotropic |
| 0,728 | 0,008 | Nootropic |
| 0,728 | 0,008 | Nerve growth factor agonist |
| 0,739 | 0,008 | Antipruritic, non-allergic |
| 0,739 | 0,008 | Antipruritic |
| 0,728 | 0,008 | Antiischemic, cerebral |
| 0,728 | 0,008 | Nerve growth factor agonist |
| 0,728 | 0,008 | Amyotrophic lateral sclerosis treatment |
| 0,728 | 0,008 | Nerve growth factor agonist |
| 0,739 | 0,008 | Allergic conjunctivitis treatment |
| 0,739 | 0,008 | Antipruritic |
| 0,768 | 0,006 | Tocolytic |

## Linalool

16 Possible activities at Pa > 70%

| Pa | Pi | Activity |
|---|---|---|
| 0,776 | 0,018 | Hypolipemic |
| 0,776 | 0,018 | Lipid metabolism regulator |
| 0,763 | 0,022 | Cholesterol synthesis inhibitor |
| 0,763 | 0,022 | Anticholelithogenic |
| 0,763 | 0,022 | Cholesterol synthesis inhibitor |
| 0,763 | 0,022 | Atherosclerosis treatment |
| 0,763 | 0,022 | Cholesterol synthesis inhibitor |
| 0,969 | 0,004 | Antiulcerative |
| 0,969 | 0,004 | Mucomembranous protector |

0,825 0,006 Skin irritations, moderate
0,714 0,008 Eye irritation, weak

## Safrole

18 Possible activities at Pa > 70%

**Pa Pi Activity:**

0,951 0,006 Antiviral
0,951 0,006 Antiviral (HIV)
0,951 0,006 Membrane integrity agonist
0,951 0,006 Membrane integrity agonist
0,951 0,006 Antipruritic
0,951 0,006 Membrane integrity agonist
0,951 0,005 Antiinflammatory
0,951 0,006 Membrane integrity agonist
0,918 0,005 Integrin antagonist
0,918 0,005 Antineoplastic
0,814 0,013 Antineoplastic (brain cancer)
0,918 0,005 Integrin antagonist
0,869 0,004 Antiparkinsonian
0,869 0,004 Neurotransmitter uptake inhibitor
0,765 0,007 Cognition disorders treatment
0,765 0,007 Alzheimer's disease treatment
0,765 0,007 Neurotrophic factor enhancer
0,765 0,007 Neurotrophic factor enhancer
0,951 0,006 Dermatologic
0,951 0,006 Antieczematic
0,951 0,006 Membrane integrity agonist
0,951 0,006 Antiseborrheic
0,951 0,006 Membrane integrity agonist
0,951 0,004 Psychotropic
0,781 0,008 Anxiolytic
0,781 0,008 GABA A receptor antagonist
0,781 0,008 Antidepressant
0,781 0,008 GABA A receptor antagonist
0,951 0,004 Antiepileptic
0,951 0,006 Membrane integrity agonist
0,869 0,004 Neurotransmitter uptake inhibitor
0,781 0,008 GABA A receptor antagonist
0,918 0,005 Antiasthmatic
0,918 0,005 Integrin antagonist
0,918 0,005 Inflammatory Bowel disease treatment
0,918 0,005 Integrin antagonist
0,918 0,005 Antiosteoporotic
0,918 0,005 Integrin antagonist
0,918 0,005 Antithrombotic
0,918 0,005 Integrin antagonist
0,779 0,021 Neuroprotector
0,768 0,015 Antiischemic
0,869 0,007 Pulmonary hypertension treatment
0,707 0,018 Antiischemic, cerebral

## Cineole

12 Possible activities at Pa > 70%

**Pa Pi Activity**

0,758 0,006 Antitoxic
0,758 0,006 Hepatoprotectant
0,758 0,006 Liver fibrosis treatment
0,758 0,006 Hepatoprotectant
0,944 0,004 Hypolipemic
0,944 0,004 Cholesterol antagonist
0,715 0,082 Antidiabetic
0,715 0,082 Phosphatase inhibitor
0,781 0,006 Cardiotonic
0,781 0,006 Heart failure treatment
0,781 0,006 Adenylate cyclase stimulant
0,781 0,006 Adenylate cyclase stimulant
0,742 0,008 Autoimmune disorders treatment
0,742 0,008 Multiple sclerosis treatment
0,715 0,082 Antineoplastic
0,715 0,082 Phosphatase inhibitor
0,781 0,006 Ophthalmic drug
0,781 0,006 Antiglaucomic
0,781 0,006 Adenylate cyclase stimulant
0,944 0,004 Atherosclerosis treatment
0,944 0,004 Cholesterol antagonist
0,721 0,009 Cognition disorders treatment
0,721 0,009 Alzheimer's disease treatment
0,721 0,009 Neurotrophic factor enhancer
0,721 0,009 Neurotrophic factor enhancer
0,781 0,006 Myocardial ischemia treatment
0,781 0,006 Adenylate cyclase stimulant
0,781 0,006 Antithrombotic
0,781 0,006 Adenylate cyclase stimulant
0,877 0,004 Choleretic
0,715 0,007 Hepatic disorders treatment
0,807 0,006 Antidyskinetic

## Discussion

PASS Inet predicts biological activity spectrum on the basis of structural formula of the compound. The compounds are considered equivalent in PASS if they have the same molecular formulae and the same set of MNA descriptors. Since the MNA descriptors do not represent the stereochemical peculiarities of a molecule, the compounds, which have only stereochemical differences in the structure, are formally considered equivalent. The equivalent structures are excluded from the training set during the PASS Inet prediction. The result of prediction is presented as the list of activities with appropriate Pa and Pi, sorted in descending order of the difference (Pa-Pi)>0.

Pa and Pi are the estimates of probability for the compound to be active and inactive respectively for each type of activity from the biological activity spectrum. Their values vary from 0.000 to 1.000. It is reasonably that only those types of activities may be revealed by the compound, which Pa > Pi and so they are put into the biological activity spectrum.

If Pa > 0.7 the compound is very likely to reveal this activity in experiments, but in this case the chance of being the analogue of the known pharmaceutical agents for this compound is also high.

If 0.5 < Pa < 0.7 the compound is likely to reveal this activity in experiments, but this probability is less, and the compound is not so similar to the known pharmaceutical agents.

If Pa < 0.5 the compound is unlikely to reveal this activity in experiments, but if the presence of this activity is confirmed in the experiment the compound might be a New Chemical Entity.

Thus, in planning experiments and choosing the activities on which the compound has to be tested, one should have in mind the necessity of balancing between the novelty of pharmacological action and the risk to obtain negative results in experimental testing. Certainly, one will also take into account the particular interest in some kinds of activity, experimental facilities, etc. We may use PASS for the prediction of the biological activity spectrum for existing compounds and compounds, which are only planned to synthesize.

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