Title: COMPOSITION OF MONOTERPENOIDS FOR THE TREATMENT OF CANCER

Abstract: The invention concerns use of a composition for the treatment and prophylaxis of cancer in a mammal. The composition comprises a mixture of 30% - 80% of at least one compound having the formula (I) (Formula (I)) and 10% to 40% of at least one compound of the formula (II) (Formula (II)) wherein the substituents are as defined in the description. The invention also relates to methods for the treatment and prophylaxis of cancer and also use of the composition in the preparation of a medicament for treatment or prophylaxis of cancer.

Fig. 1

(Continued on next page)
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FIELD OF THE INVENTION

The present invention relates to agents and methods for use in cancer therapy.

BACKGROUND OF THE INVENTION

Treatment of human cancer is an area of clinical medicine that has and received considerable attention. Conventional cancer treatment methods include chemotherapy, radiation and surgery, each of which has its own disadvantages. The well recognized disadvantage of chemotherapy is its non-selectivity between normal and cancer cells. With a view to addressing this problem of non-selectivity, current research is investigating the use of biochemical agents that maybe specific to cancer cells. There are two broad classes of such agents. The first is directed at binding cancer specific receptors on the cell surface. The second type is aimed at the survival and apoptosis pathways.

However, many pathways and proteins control cell death and survival. This complexity significantly adds to the problems associated with finding an effective agent. Still further, the types of receptors and deregulated pathways are generally cancer dependent. This means that chemotherapeutic agents are cancer specific. For example, is well known that agents useful for treating hormone related cancers such as breast and prostate would be ineffective in controlling other types of cancers such as squamous cell carcinomas or adenocarcinomas.

To date, there have been many thousands of compounds that have been undergone in vitro testing for the treatment of cancer. Whilst many of these compounds have been shown to have cytotoxic activity against cancer cells in vitro, they have failed to be adopted for cancer treatment. A major reason for such failure is unacceptable toxicity to normal cells and/or side effects.
It is clearly desirable to investigate new anti-cancer agents and therapies that are selective for cancer cells and may also be effective against different forms of cancer.

SUMMARY OF THE INVENTION

A method for the treatment or prophylaxis of cancer in a patient comprising administering to the patient a therapeutically effective amount of a composition comprising:

(a) 30% - 80% of at least one compound having the formula 1

\[
\begin{align*}
R^1 & \quad (R^1)_{o} \\
R^2 & \quad (R^2)_{o} \\
R^3 & \quad (R^3)_{o} \\
R^4 & \quad (R^4)_{o} \\
R^5 & \quad (R^5)_{o} \\
R^6 & \quad (R^6)_{o}
\end{align*}
\]

wherein \(\cdots\) is \(\cdots\) or \(\cdots\), but consecutive \(\cdots\) cannot be \(\cdots\);

the cyclohexane ring may be saturated or unsaturated with any degree of unsaturation provided that when a \(\cdots\) attached to the ring is = the ring carbon to which the \(\cdots\) is attached is unsaturated;

one of \(R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8\) or \(R^9\) is \(\text{OH}\), and each of the remaining \(R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8\) and \(R^9\) is \(\text{H}\);

\(o\) is 0 when the \(\cdots\) to which \(R^1, R^4, R^5\) or \(R^9\) is attached is = and \(o\) is 1 when the \(\cdots\) to which \(R^1, R^4, R^5\) or \(R^9\) is \(\cdots\);

(b) 10% to 40% of at least one compound of formula 2
Formula 2

wherein --- is ---, --- or △, but consecutive --- cannot be
--- or ○;

the cydohexane ring may be saturated or unsaturated with any degree of
unsaturation provided that when a --- attached to the ring is ○ or
△ the ring carbon to which the --- is attached is unsaturated;

X is -O- or -O-O-;

Y is -O- or -O-O-

n is 0 or 1, m is 0 or 1, but n and m cannot both be 1 and neither n or m can
be 1 if the --- attached to the ring is ○ or △

R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸ or R²⁹ are each independently selected
from H, OH, OOH, OC-OR, OR; or an adjacent pair of R²¹, R²², R²³, R²⁴, R²⁷

or R²⁸ may join to form an epoxide or ○; wherein any one of R²²,
R²³, R²⁷, R²⁸ or R⁹ may further be =0, provided that =0 is attached to an
unsaturated carbon; \( o \) is 0 when the \( \longrightarrow \) to which \( R^{21} \), \( R^{24} \) or \( R^{26} \) is attached is \( \bigtriangleup \) or \( \bigcirc \) and \( o \) is 1 when the \( \longrightarrow \) to which \( R^{21} \), \( R^{24} \) or \( R^{26} \) is \( \bigtriangleup \) and

\[ R \text{ is a } \text{C}_1 \text{ to } \text{C}_3 \text{ alkyl; } \]

wherein the compound contains at least two Oxygen atoms; and

(c) from 0 to 20% of at least one compound selected from the group consisting of a sesquiterpene, a sesquiterpene alcohol, a sesquiterpene epoxide, p-cymene, an oxygenated cyclohexane, an oxygenated cyclohexene, and a monoterpene, wherein the amount of any monoterpenes in the fraction does not exceed 5% of the total composition.

The present inventor has surprisingly discovered that the composition of the invention is not only effective but effective against a wide range of cancers. This is contrary to conventional cancer therapies that are generally specific to a particular cancer. The advantages of a non-specific cancer treatment may be readily recognized. Still further screening studies have shown that the composition inhibits growth of some cell lines and induces apoptosis in others. Again this is unusual as inhibition of cell growth and apoptosis are governed by different mechanisms. Conventional cancer drugs act by one mechanism or the other but not both. Thus, without wishing to be bound by theory, the present inventor believes that the mechanism of action, although not understood, is distinct from conventional therapies.

A still further surprising result is that the composition of the present invention has been observed to prevent cancer developing in mice injected with lung cancer cells. Thus, the present invention also relates to a method of minimizing the risk of a person at high risk from developing cancer or minimizing the risk of cancer reoccurring by administering an effective amount of the above composition. Typically, the dose is in the range of 10mg/kg to 100mg/kg, typically between about 20mg/kg to about 60 mg/kg. Typically the dose is taken orally on a daily basis.
Persons at high risk of cancer include smokers which is a risk factor for cancers of the lungs, larynx (voice box), mouth, throat, oesophagus, kidneys, bladder, colon, and several other organs and those that are genetically pre-disposed to certain types of cancer. Other at risk persons are those in remission who are at risk of the cancer re-occurring.

Thus, a further method of the present invention includes genetically testing a person and assaying if they are genetically disposed to cancer and administering a prophylactically effective amount of the above composition.

In the present specification and claims, the term % refers to the percentage as determined by chromatographic analysis, unless indicated otherwise. Chromatographic methods for the analysis of compounds are well known in the art of natural product chemistry and aroma chemistry. A particular suitable method of analysis is absorption or normal phase chromatography that separate components according to their polarity. HPLC analysis on a diol bonded silica gel is preferred.

The present inventor has surprisingly discovered that the composition of the invention is effective against a broad range of cancers at concentrations that may be considered suitable for therapy.

The compounds of formulas 1 and 2 include oxygenated derivatives of monoterpenes having a p-menthane skeleton. Monoterpenes are widely found in natural products and have the formula $C_{10}H_{16}$. The compounds of formulas 1 and 2 may be obtained or derived from known natural sources of monoterpenes or may be synthesized. Sources of monoterpenes and their oxygenated derivatives include but are not limited to eucalyptus oil, oil of cajeput, oil of camphor, oil of cardamom, tea tree oil, oil of cedar and oil of cypress. Suitable methods of extraction are known to those of skill in the art.

The oxygenated compounds of formula 1 and formula 2 may be obtained by oxidation of parent monoterpenes. Suitable starting monoterpenes include, \( \ldots \)
pinene, β pinene, sabinene, myrcene, α phellandrene, β phellandrene, terpinene, β terpinene, γ terpinene, limonene, α limonene diepoxide and terpinolene. These compounds are naturally occurring and may be isolated from a variety of plant sources.

Many of these compounds are commercially available in an essentially pure form. Oxidation of monoterpenes is used to produce compounds for use in the flavour and perfumery industry. Oxidation of monoterpenes is well known in the field of organic flavour chemistry.

α-terpinene is a suitable starting material as it may readily be oxidised with molecular oxygen via a diels alder cyclization of the 1,3-diene to produce the menth-2-ene, 1,4-endoperoxide (reaction 1 in Scheme 1 below). The peroxide is a useful intermediate as it may undergo further reaction with water to produce 1-hydroperoxy-4-hydroxy-menth-2-ene (reaction 2). Subsequent reduction with lithium hydroxide for example yields 1,4-dihydroxymenth-2-ene (reaction 3).

Scheme 1

α-terpinene may also be oxidized with t-butyl chromate according to the procedure described by Suga et al. "Stereochemical Studies of monoterpenic compounds III. Stereochemistry and intramolecular hydrogen bonding of 1-hydroxy-p-menth-3-en-2-one and its reduction products, Bulletin of the Chemical Society of Japan, 41, 944-048 (1968). The reaction produces 1-hydroxy-p-menth-3-en-2-one (reaction 4) which may subsequently be hydrogenated (reaction 5) and reduced (reaction 6) or reduced (reaction 7) and hydrogenated (8) as shown in scheme 2 below.
Scheme 2

Terpinene-4-ol is also a suitable starting product and may be oxidised to 1,2,4-trihydroxy menthane by a number of reactions, one of which is as shown below in scheme 3 (Cristea, et al. "Stereoselective trans-dihydroxylation of terpinen-4-ol: synthesis of some stereoisomers of p-menthane-1,2,4-trior. Tetrahedron: Asymetry, 13, (9) 915-918).

Scheme 3

1,4-dihydroxymenth-2-ene can be prepared from ascaridole by first hydrolysing ascaridole to menth-2-ene-1,4-endoperoxide followed by reduction to give the product compound.
Oxidation of monoterpenes often results in a mixture of compounds. In the compositions and methods of the present invention, mixtures of compounds of the invention may be tolerated where components of the mixture either are inactive and non-toxic or present in very low concentrations. In some cases, it may not be necessary for the parent monoterpenes to be chemically or chirally pure.

Whilst not wishing to be bound by theory, the present inventor believes that there is considerable tolerance in the relative amounts of compounds of the respective formulas that may be found in the composition, whilst still providing an effective composition against cancer. Whilst not wishing to be bound by theory, the present inventor believes that it is the relative amounts of the mono, di and tri oxygenated compounds having the basic skeleton of formula 1 and 2 that are important. It is also believed, without wishing to be bound by theory, that the range of compounds may be at least partly responsible for the efficacy of the present composition against cancers of different types.

Preferred compounds of formula 1 include α-terpineol (1), β-terpineol (2), γ-terpineol (3), terpinene-4-ol (4), menthol (5), thymol (6), carvacrol (7), carveol (8), isopipertinol (9), perillyl alcohol (10), 8-hydroxy-p-cymene (11), isopulegol (12), limonene-10-ol (13) and dihydrocarceol (14) and 4-isopropyl-1-methylcyclohex-e-enol (15)
A preferred composition contains terpinene-4-ol as the major constituent. Terpinene-4-ol is found in nature and is a major constituent of the tea tree oil. Terpinene-4-ol is also available commercially in the racemic form, and as the R and S isomers. In tea tree oil the chiral purity has been found to be (+)-(4R)-Terpineol 75% and (-)-4S-a>Terpinen4-ol 25% (Burfield and Sheppard Hanger, "super Clone 88 - <elalecu Alternifolia - what is its value?", http://atlanticinstitute.com/teatree.pdf). Preferably, terpinene-4-ol is present from about 40% to about 70%, preferably between about 45% to about 65%,
preferably between about 48% to about 60% of the composition. Preferably the chiral purity of the terpinene-4-ol reflects that found in nature.

Preferably, the composition includes at least two compounds of formula 1. Preferably, the second compound is \( \alpha \)-terpineol. A typical composition comprises between about 40% to about 70% preferably between about 45% to about 65%, preferably between about 48% to about 60% terpinene-4-ol and about 2% to about 15%, preferably between about 4% to about 12%, most preferably between about 5% to about 10% \( \alpha \)-terpineol.

In one embodiment, the compounds of formula 1 consist essentially of terpinene-4-ol and \( \alpha \)-terpineol.

As used herein, the phrase "consisting essentially of" limits the scope of the related disclosure or claim to the specified compounds, plus those that do not materially affect the basic and novel characteristic(s) of the disclosed and/or claimed subject matter. For example, a composition in which the compounds of formula 1 "consist essentially of terpinene-4-ol and \( \alpha \)-terpineol means that the recited compounds together represent at least 80%, or at least 85%, or at least 90% or at least 95% or at least 97.5% or at least 99% of the compounds of formula 1.

Suitable compounds of formula 2 include the following:
Preferably, the composition includes between about 10% to about 40%, preferably between about 15% to about 35%, preferably between about 20 to about 30% of di and tri-oxygenated compounds of formula 2.
Preferably the ratio of di-oxygenated to tri-oxygenated compounds is between about 1:1 to 5:1, preferably between about 1.5:1 to about 4:1, most preferably between about 2:1 to about 3:1.

An especially preferred composition comprises a fraction of compounds of formula 2 that comprises between about 1 to about 4%, preferably between about 2 to about 3% 2-hydroxy-1,4-cineole, between about 5% to about 15%, preferably between about 6% to about 12%, preferably between about 8% to about 10% 1,4-dihydroxy-menth-2-ene, between about 0.5% to about 5%, preferably between about 1% to about 4% 1,2-dihydroxy-menth-3-ene and between about 1 to about 10%, preferably between about 2% to about 8%, preferably between about 3% to about 6% 1,2,4-trihydroxy-menthane.

Some of these compounds are naturally occurring and are found in essential oils. 2-hydroxy-1,4-cineole may be found in extracts from Hibiscus sabdariffa L. It is also available commercially. Cymenol is found in sage essential oil (Salvia officinalis) and essential oils of Jumiperus genus plants, 4,6-dihydroxy-p-menth-1-ene is found in oil of cumin, 1,4-dihydroxy-p-menth-2-ene in peppermint oil, 1,2-dihydroxy-p-menth-3-ene is found in Ferula jaeschchkeana and 1,2,4-trihydroxy-p-menthane is found in the oil of Zanthoxylum bundruga fruits.

The composition may also contain up to 20% of compounds other than those of formulas 1 and 2. These other compounds may include sesquiterpenes and oxygenated derivatives thereof, oxygenated cyclohexane, oxygenated cyclohexene, p-cymene and low levels (less than 5%) of monoterpenes. It will be appreciated that any additional compounds should be non-toxic or be present in below toxic levels. In one embodiment, the composition can contain up to 15wt% p-cymene.

The term oxygenated cyclohexene refers to any compound having a cyclohexene skeleton that is substituted with one or more oxygen groups such as =O, -OOH, or OH. The cyclohexene may further be substituted with a methyl or ethyl. A preferred compound is 4-methyl - 4-hydroxy - cyclohex-3-enone.
The term oxygenated cyclohexane refers to any compound having a cyclohexane skeleton that is substituted with one or more oxygen groups such as =0, -OOH, or OH. The cyclohexane may further be substituted with a methyl or ethyl.

The composition may also contain up to 5% of a compound of formula 3:

![Chemical structure](image)

**Formula 3**

wherein ——— is ———, ——— or ———, but consecutive ——— cannot be ——— or ———.

R\(^1\) and R\(^3\) are each independently selected from H, OH, OOH, OC=OR, OR, R\(^3\) may further be =O provided that the =O is not attached to an unsaturated carbon; R\(^3\) is selected from the group consisting of CO, COOH, COH, COOR, COR; R\(^1\) and R\(^3\) may join to form a lactone;

o is 0 when the ——— to which R\(^1\) is ——— or ——— and o is 1 when the carbon to which R\(^3\) is ——— and

R is a C\(_1\) to C\(_3\) alkyl.

The compounds of formula 3 may be formed by an oxidative ring opening reaction of a parent monoterpane. This may occur as a by-product of the oxidation reaction that produces compounds of formula 1. Especially preferred compounds include cis and/or trans 6-oxo-3-isopropyl-hept-2-enal and 6-oxo-3-isopropylheptenoic acid.
Stereoisomers:
Certain compounds of the invention contain chiral centres. Both racemic and
diasteromeric mixtures, as well as the individual optical isomers isolated or
synthesized, substantially free of their enantiomeric or diastereomeric partners,
are all within the scope of the invention. The racemic mixtures may be
separated into their individual, substantially optically pure isomers through well-
known techniques, such as the separation of diastereomeric salts formed with
optically active adjuncts, e.g., acids or bases followed by conversion back to the
optically active substances. The desired optical isomer may be synthesized by
means of stereospecific reactions, beginning with the appropriate stereoisomer
of the desired starting material.

Prodrugs:
Prodrugs of the compounds of the invention are also contemplated. The terms
"pro-drug" and "prodrug" are used interchangeably herein and refer to any
compound which releases an active parent compound according to Formula I, 2
or 2a in vivo when such prodrug is administered to an animal. Prodrugs may be
prepared by modifying one or more functional group(s) present in the compound
of Formula I or 2 in such a way that the modification(s) may be cleaved in vivo to
release the parent compound.

Prodrugs include compounds of Formulas I, 2 or 3 wherein a hydroxy, carboxy
or carbonyl group in a compound of Formulas I, 2 or 3 is bonded to any group
that may be cleaved in vivo to regenerate the free hydroxyl group. Examples of
prodrugs include, but are not limited to, esters (e.g., acetate,
dialkylaminoacetates, formates, phosphates, sulfates, and benzoate derivatives)
of hydroxy functional groups and esters groups (e.g. ethyl esters,
morpholinoethanol esters) of carboxyl functional groups, oximes, acetics, ketals
and enol esters of ketone and aldehyde functional groups in compounds.

The pharmaceutical compositions of the present invention can be
manufactured by methods well known in the art such as conventional mixing,
dissolving, encapsulating, lyophilizing or emulsifying, among others. The
compositions can be in the form of, for example, granules, powders, tablets, capsules, syrup, suppositories, injections, emulsions, elixirs, suspensions or solutions. The instant compositions can be formulated for various routes of administration, for example, by oral administration, by transmucosal administration, by rectal administration, or subcutaneous administration as well as intrathecal, intravenous, intramuscular, intraperitoneal, intranasal, intraocular or intraventricular injection. The compound or compounds of the instant invention can also be administered in a local rather than a systemic fashion, such as injection as a sustained release formulation. The following dosage forms are given by way of example and should not be construed as limiting the instant invention.

For oral, buccal, and sublingual administration, powders, suspensions, granules, tablets, pills, capsules, gelcaps, and caplets are acceptable as solid dosage forms. These can be prepared, for example, by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts or tautomers thereof, with at least one additive or excipient such as a starch or other additive. Suitable additives or excipients are sucrose, lactose, cellulose sugar, mannitol, maltitol, dextran, sorbitol, starch, agar, alginates, chitins, chitosans, pectins, tragacanth gum, gum arabic, gelatins, collagens, casein, albumin, synthetic or semi-synthetic polymers or glycerides, methyl cellulose, hydroxypropylmethylcellulose, and/or polyvinylpyrrolidone. Optionally, oral dosage forms can contain other ingredients to aid in administration, such as an inactive diluent, or lubricants such as magnesium stearate, or preservatives such as paraben or sorbic acid, or anti-oxidants such as ascorbic acid, tocopherol or cysteine, a disintegrating agent, binders, thickeners, buffers, sweeteners, flavoring agents or perfuming agents. Additionally, dyestuffs or pigments may be added for identification. Tablets and pills may be further treated with suitable coating materials known in the art.

Liquid dosage forms for oral administration may be in the form of pharmaceutically acceptable emulsions, syrups, elixirs, suspensions, slurries and solutions, which may contain an inactive diluent, such as water.
Pharmaceutical formulations may be prepared as liquid suspensions or solutions using a sterile liquid, such as, but not limited to, an oil, water, an alcohol, and combinations of these. Pharmaceutically suitable surfactants, suspending agents, emulsifying agents, may be added for oral or parenteral administration.

For nasal or buccal administration, the pharmaceutical formulations may be a spray or aerosol containing and appropriate solvents and optionally other compounds such as, but not limited to, stabilizers, antimicrobial agents, antioxidants, pH modifiers, surfactants, bioavailability modifiers and combinations of these. A propellant for an aerosol formulation may include compressed air, nitrogen, carbon dioxide, or a hydrocarbon based low boiling solvent. The compound or compounds of the instant invention are conveniently delivered in the form of an aerosol spray presentation from a nebulizer or the like.

Injectable dosage forms generally include aqueous suspensions or oil suspensions which may be prepared using a suitable dispersant or wetting agent and a suspending agent. Injectable forms may be in solution phase or in the form of a suspension, which is prepared with a solvent or diluent. Acceptable solvents or vehicles include sterilized water, Ringer's solution, or an isotonic aqueous saline solution. Alternatively, sterile oils may be employed as solvents or suspending agents. Preferably, the oil or fatty acid is non-volatile, including natural or synthetic oils, fatty acids, mono-, di- or triglycerides.

For injection, the formulations may optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these. The compounds may be formulated for parenteral administration by injection such as by bolus injection or continuous infusion. A unit dosage form for injection may be in ampoules or in multi-dose containers.

For rectal administration, the pharmaceutical formulations may be in the form of a suppository, an ointment, an enema, a tablet or a cream for release of compound in the intestines, sigmoid flexure and/or rectum. Rectal suppositories
are prepared by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts or tautomers of the compound, with acceptable vehicles, for example, cocoa butter or polyethylene glycol, which is present in a solid phase at normal storing temperatures, and present in a liquid phase at those temperatures suitable to release a drug inside the body, such as in the rectum. Oils may also be employed in the preparation of formulations of the soft gelatin type and suppositories. Water, saline, aqueous dextrose and related sugar solutions, and glycerols may be employed in the preparation of suspension formulations which may also contain suspending agents such as pectins, carboxomers, methyl cellulose, hydroxypropyl cellulose or carboxymethyl cellulose, as well as buffers and preservatives.

The compounds may also be administered dermally. It has been observed that the compounds are readily absorbed through the skin such that dermal uptake directly into the lymphatic system by dermal application about the lymph nodes is possible.

The terms "effective amount" and "therapeutically effective amount" of a compound as used herein mean a sufficient amount of the compound or a mixture of one or more thereof, to provide the desired therapeutic or physiological effect or outcome. Undesirable effects, e.g. side effects, are sometimes manifested along with the desired therapeutic effect; hence, a practitioner balances the potential benefits against the potential risks in determining what is an appropriate "effective amount". The exact amount required will vary from subject to subject, depending on the species, age and general condition of the subject, mode of administration and the like. Thus, it may not be possible to specify an exact "effective amount". However, an appropriate "effective amount" in any individual case may be determined by one of ordinary skill in the art using only routine experimentation.
Definitions
The term "monoterpenoid" refers to a monoterpane-like substance and may be used loosely herein to refer collectively to monoterpenoid derivatives as well as monoterpenoid analogs. Monoterpenes are derived from an isoprene unit and have the formula C_{10}H_{16}. Monoterpenoids can therefore include monoterpenes, alcohols, ketones, aldehydes, esters, ethers, acids, hydrocarbons without an oxygen functional group, and so forth. It is common practice to refer to certain phenolic compounds, such as eugenol, thymol and carvacrol, as monoterpenoids because their function is essentially the same as a monoterpenoid. Although, these compounds are not technically "monoterpenoids" (or "monoterpenes") because they are not synthesized by the same isoprene biosynthesis pathway, but rather by production of phenols from tyrosine common practice will be followed herein.

The term "sesquiterpene" as used herein refers to a compound having a 15-carbon skeleton with non-linear branches. The molecular formula is C_{15}H_{24}. The term "sesquiterpenoid" refers to a sesquiterpene-like substance and may be used loosely herein to refer collectively to sesquiterpenoid derivatives as well as sesquiterpenoid analogs. Sesquiterpenoids can include sesquiterpenes, alcohols, ketones, aldehydes, ethers, acids, hydrocarbons without an oxygen functional group, and so forth.

BRIEF DESCRIPTION OF THE FIGURES
Figure 1 is a graph showing the relationship between cancer cell population and oil concentration;
Figure 2 is a one dose mean graph showing the results of a NCI 60 Cell One Dose Screen;
Figures 3 and 4 are graphs showing change in total mouse weight and change in tumor weight for in vitro mice trials and
Figure 5 is a graph showing the effect of intratumoral injection on tumor growth in mice.
DETAILED DESCRIPTION OF THE INVENTION

Toxicity Studies
A 10% aqueous solution of the tea tree extract was prepared and rat toxicity tests were conducted. The LD$_{50}$ was calculated to be 21g/kg bw of male wistar rats. This is essentially a non-toxic compound. When this value is converted to human (70)kg using a body surface area method, then the oral dose of 208.87g (2.98g/kg man) is found.

In vitro trials
NCI-60 DTP Human Tumor Cell Line Screen
MJR-2 was screened using the NCI-60 cell line screen. This screening test uses a panel of 60 different cell lines from Leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer. The results in terms of mean graph of the percent growth of treated cells is shown in figure 2. The number reported for the One-dose assay is growth relative to the no-drug control, and relative to the time zero number of cells. This allows detection of both growth inhibition (values between 0 and 100) and lethality (values less than 0). For example, a value of 100 means no growth inhibition. A value of 0 would mean 100% growth inhibition. A value of 0 means no net growth over the course of the experiment. A value of -100 would mean 100% lethality. A value of -100 means all cells are dead. It may be seen from the results that a significant number of cell lines across all cancer types showed a negative growth and three different cell lines, U251, OVCAR-3 and SN12C had a value of -100%.

Human mammary carcinoma MCF-7 cells
Samples of healthy growing human mammary carcinoma MCF-7 cells were established in 96 well microtitre culture plates in full RPMI or DMEM growth media containing 10% Fetal Calf Serum. The cells were initially established at ca 10,000 cells per well for 1 day assays and ca 5,000 cells per well for the 3 day assays. Some columns of wells in the plate were kept as controls containing media alone. Stock solutions of the oil extract at 1 to 9 parts
dissolved in either neat ethanol or DMSO were prepared to enable the oil to solubilise in the media. Serial dilutions were then prepared using complete culture media as diluents across the columns of the plate. Either 4 or 10 fold dilution series were used as indicated. The plates of cells were then returned to the 37 degree CO\textsuperscript{2} incubator for a period of either overnight or 3 days. After treatment with the oil, a metabolic indicator dye (XTT) was added into each well and the plates incubated to allow the dye to develop for a further period of 1-2 hours. The absorbance at 490nm was measured in a plate spectrophotometric reader and the data analysed. All data shown were background subtracted for the absorbance values obtained with XTT dye alone added to media. The final absorbance values were calculated as the percentage live cells relative to the cells not treated with the oil used as controls.

The IC50 values were calculated. IC50 is the concentration of agent that provides a 50% reduction in the growth of treated cells as compared to the untreated cells as control. The results are shown in Table 3 below:

| TABLE 3 |
|------------------|------------------|------------------|------------------|
| 3 day IC50       | 3 day IC50       | 1 day IC50       | 1 day IC50       |
| Ethanol (4 dilution) | DMSO (4 dilution) | Ethanol (10 dilution) | DMSO (10 dilution) |
| 0.007%           | 0.02%           | 0.015%           | 0.02%           |

These results show that the oil is cytotoxic to cancer cells.

Human Cervical Cancer Cells (Hela); Human colon Cancer cells (HT29) and Human colon cancer Cells (SpcA-1).

Studies were conducted observing the effect of cancer cell concentration on the above three cell lines after treatment with increasing amounts of the composition of the invention. The results are shown in Figure 1.

It may be seen that at a concentration of 0.008%, the composition was effective in killing cells of all cancer cell lines. That a single agent shows a similar effect across three distinctly different cell line is surprising. This suggests a non-
cancer specific mode of action, although showing a selective toxicity to cancer as compared to normal cells as shown in the toxicity studies.

These results may be compared to those as reported in an article published by Calcabriti et al in The Journal or Investigative Dermatology 3004 p 349 - 360. In this study, the effect of a conventional tea tree oil, having a composition similar to the typical composition referred to in Table 1 above on melanoma cells was studied. A concentration of 0.01% (i.e. higher than 0.008%) showed no effect on the growth of normal melanoma M14WT cells and decreased the growth (but did not decrease the number) of resistant M14ADR cell lines. A concentration of 0.03% was required to reach a zero cell number and the time period for this was 8 days for M14WT cells and 3 days for M14 ADR cells.

The present inventor believes that this contrasts significantly to that of the present invention showing a kill concentration of 0.008% after only 1 day for three different cancer cell lines. Further, this prior art teaches that terpinen-4-ol is the active anti-neoplastic agent. Whilst not wishing to be bound by theory, the present inventor believes, that whilst terpine-4-ol may exhibit some effect, the extrapolated therapeutic dose would be unacceptably toxic. The present inventor believes that the observation that the above trials show a significantly improved anti-neoplastic effect with similar levels of terpinene-4-ol as the prior art

In vivo studies

Part 1

In vivo studies using xenograft cancer mouse model produced from SpcA1 cancer cells and SCID mice were performed. 3 groups of experimental animals were used for the study namely control, treatment 1 and treatment 2. Each group contains 4 SCID mice. On the back of each mouse, four lung cancer cell (1 x 10^5 of Spc-A1 cancer cells)-Matrigel mixtures were injected subcutaneously. After 2 weeks when the tumor grew to about 5mm cross size, 20mg/kg of MJR-2 was injected intraperitoneally into each mouse from treatment 1 group every 24 hours, meanwhile 60 mg/kg of MRJ-2 was injected in each mouse from
treatment 2 group. On contrary, DMSO was injected intrapertitoneally into animals form the control group. The treatment was performed for a period of 2 weeks.

During the process of treatment, mice weights from all groups were recorded to investigate if MJR-2 would exert any toxic effects on animals. After 2 weeks, mice were sacrificed by CO2 asphyxiation. Tumor and lung samples from all animals were taken for immunohistochemistry study. The results showed that, as compared to the control group, tumors of mice in both treatment group showed inhibited growth during the course of treatment. However, complete tumor regression was not observed during the course of treatment. This is possible due to insufficient concentration of MJR-2 used. Meanwhile, animals from both treatment groups did not show significant weight loss as compared to the animals in the control group. In addition, no other side effects in MJR-2 treated animals were detected indicating that the concentrations of MAC used were not toxic to animals and higher concentrations of MJR-2 can be trailed for later experiments.

No lung metastatic tumor nodules were detected when animal lungs were removed and this was further confirmed by H and E staining.

Hypoxia levels of mice tumors from both control and treatment group were investigated. Tumor hypoxia plays a pivotal role in tumor development. Immunohistochemical studies showed similar staining pattern of HIF-alpha, which accumulates within hypoxic tumor microenvironment suggesting that similar levels of tumor hypoxia were present in all animal tumors.

The level of VEGF in the tumor was also investigated by immunohistochemical study. Increased level of VEGF is a hall mark of tumor angiogenis. As for tumor hypoxia, tumor angiogenesis is also extremely important in the development of solid tumors, therefore many therapies aimed at interfering with tumor angiogenesis have been developed for anti-cancer properties. The results indicated high levels of VEGF in the tumors of control animals.
Part 2
To further elucidate if MJR-2 helps prevent tumor form growing another *in vivo* study using the same xenograft mouse model was performed. In this study, three animal groups were used including the control, treatment 1 and treatment 2 groups. For the control group no MJR-2 was injected. 3 weeks after cancer cells were injected, all the animals developed tumors with an average size of 3.8mm. On the other side, 20 mg/kg (for treatment 1 group) or 60 mg/kg (for treatment 2 group) of MJR-2 was injected intraperitoneally right after the tumor cells were inoculated subcutaneously. Then the MJR-2 was injected every 2 hours. After 3 weeks of treatment, no tumors were observed on all animals indicating MJR-2 has affirmative inhibitory effect on tumor growth at both concentrations.

Both *in vitro* and *in vivo* studies showed that MJR-2 has anticancer ability at reasonable concentrations that did not induce toxic effects in experimental animals. Furthermore, these studies showed that MJR-2 inhibited growth of implanted SpcA1 tumor cells from growing in immunodeficient mice indicating it has preventative effects on tumor growth.

Intratumoral injection studies
A study was conducted to investigate the efficacy of 3% v/v MJR-2 injected intratumorally *in vivo* murine breast cancer model.

Five female FVB/N *c-neu* mice were implanted subcutaneously with $1 \times 10^6$ NeuTL cells (a synergic murine breast cancer cell line) harvested form an implanted NeuTL tumor. Tumor growth was monitored daily and treatment with MJR-2 initiated once tumors were palpable (Day0). MJR-2 was administered as a 3% v/v solution suspended in 1%w/v vitamin E. Four mice received 50$\mu$I intratumoral injections of 3% v/v solution MJR-2 (corresponding to 1.5 $\mu$I of neat MJR-2) administered every 3 days. One mouse received no treatment and served as a control. Tumor growth was monitored using manual callipers and ultrasound.
Figure 5 shows the results in terms of a graph of tumor area v days post injection. It may be seen that for tumors having an area of less than $100\text{mm}^2$ that MRJ-2 was effective at inhibiting tumor growth. Tumors of over $100\text{mm}^2$ appeared to grow at the same rate as the control. It is likely that at this size, the amount of MRJ-2 injected is no longer capable of diffusing into the tumor to inhibit growth. It is believed that this may be addressed with a higher dose of MRJ-2, multiple injection sites or both.

No significant adverse effects were observed in the mice following intratumoral delivery and appetite and weight gain were normal.

**Antioxidant trial**

An ORAC antioxidant study was conducted by Brunswick Laboratory according to the protocol described in Huang et al. "High throughput Quantitation of Peroxyl Radical Scavenging Capacity in Bulk Oils by monitoring Oxygen Consumption Rates", Journal of Agricultural and Food Chemistry 2006, 54, 5299-5305.

The ORAC analysis provides a measure of the scavenging capacity of antioxidants against the peroxy radical, which is one of the most common reactive species found in the body. Vitamin E is used as the calibration standard and the ORACoil result is expressed as micromole vitamin E equivalent (VE) per litre.

The result for the MJR-2 as described above as compared to other antioxidants is shown below in Table 4:
It may be seen that the oil of the invention shows a remarkably high anti-oxidant activity. Whilst not wishing to be bound by theory, the present inventor believes that this high anti-oxidant activity has an anti-carcinogenic effect.

**Pharmaceutical compositions**

**Capsules were prepared as follows:**

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MJR-2</td>
<td>50 mg</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>650mg</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td><strong>800mg</strong></td>
</tr>
</tbody>
</table>

**Suppositories were prepared as follows:**

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>cocoa butter</td>
<td>70 grams</td>
</tr>
<tr>
<td>soya oil</td>
<td>5 grams</td>
</tr>
<tr>
<td>MJR-2</td>
<td>25 grams</td>
</tr>
</tbody>
</table>

The above mixture makes 1 gram suppositories having an oil content of 0.250 grams.

**Cervical Cancer**

A patient presented with a re-occurrence of cervical cancer. The patient had contracted cervical cancer 3 years previously and had undergone chemo and
radiation therapy. The procedure had a number of undesirable side effects that left her with a permanent colostomy bag and rectal ulcers.

The patient experienced a relapse of the cancer. Treatment was begun using the method of the present invention. The patient was administered the extract as described above in relation to Table 1. 150mg was administered orally and 250mg rectally on a daily basis for a period of 2 months. After this time period, there was no longer any evidence of cancerous cells as tested by pap smear and cervical scrap.

Treatment was continued for a further 2 months after which time blood tests were performed. Blood chemistry indicated no evidence of cancer.

**Prostate Cancer**

A patient was diagnosed with prostate cancer with a PSA reading of 4.2µ (normal range is less than 3.5) with physical examination showing many small cancer growths. His physician had recommended surgery.

The patient was treated with a daily oral dose of 150mg and a daily rectal dose of 250mg. After daily treatment for 60 days, an MRI scan showed no sign of cancer cells in the prostate and the PSA values had dropped from 4.2pg/L to 2.7µg/L. Based upon these results, it was decided that surgery was no longer necessary.

Treatment was continued for a further 2 months after which time blood test were performed. Blood chemistry showed the PSA values had dropped to well below 4.2µg/L indicated no cancer activity.

**Colon Cancer**

A patient presented with colon cancer. The patient's CRP was 19mg/L and she was losing weight. Surgery had been recommended but the patient did not want the surgery.
The patient was treated with a daily oral dose of 50mg and a daily rectal dose of 250mg. After this time, her CRP level had dropped to 8mg/L and her weight had stabilized.

Treatment was continued for a further 2 months.

The indications were that the growth of the cancer had been stopped. The patient then agreed to have the surgery performed. The surgeons believe the surgery to be successful.

It may be seen that the method of the present invention was successful in treating or controlling different forms of cancer. That a single agent is successful against different forms of cancer is itself surprising.

None of the patients reported any adverse side effects of the therapy and to the contrary reported an improvement in their general well-being. Whilst not wishing to be bound by theory, the present inventor is of the view that the composition is effective in stimulating the immune system.

A further advantage of the low or negligible toxicity of the compounds as used in the invention is the safety for those preparing and administering the formulations. The hazards assisted with administrating chemotherapeutic agents are well known. Still further, in many cases, there is a narrow margin between a therapeutic and a toxic dose of chemotherapeutic agents. This would not be the case with the methods of the present invention, thereby adding a further level of safety to the patient and minimization of undesirable side effects.

It may be seen that in the early stages, the method of the present invention may be successful in halting the growth of the cancer, or even removal of the cancer. At later stages of disease, the method may be successful in controlling the growth of the cancer. The present invention may also be suitable in the treatment of metastatic cancers of unknown primary origin.
necessary to know the nature of a primary cancer, as the treatment depends upon the type of primary cancer. For example, where cancer in the lung is caused by the spread of breast cancer cells, the cancer is not lung cancer but metastatic breast cancer. However, the compositions of the present invention are active against a range of cancer types.

It will be appreciated that various changes and modifications may be made to the present invention as described and claimed herein, without departing from the spirit and scope thereof.
CLAIMS

1. A composition comprising:

   (a) 30% - 80% of at least one compound having the formula 1

   \[ R^6 \]
   \[ R^8 \]
   \[ R^9 \]
   \[ R^1 \]
   \[ R^2 \]
   \[ R^3 \]
   \[ R^4 \]
   \[ R^5 \]
   \[ R^7 \]

   wherein \( \sim \) is \( \sim \) or \( = \), but consecutive \( \sim \) cannot be \( \sim \);

   the cyclohexane ring may be saturated or unsaturated with any degree of
   unsaturation provided that when a \( \sim \) attached to the ring is \( \sim \) the ring
   carbon to which the \( \sim \) is attached is unsaturated;

   one of \( R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 \) or \( R^9 \) is OH, and each of the remaining \( R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 \) and \( R^9 \) is H;

   o is 0 when the \( \sim \) to which \( R^1, R^4, R^5 \) or \( R^9 \) is attached is \( \sim \) and o is 1
   when the \( \sim \) to which \( R^1, R^4, R^5 \) or \( R^9 \) is \( \sim \);

   (b) 10% to 40% of at least one compound of formula 2

   \[ R^{26} \]
   \[ R^{28} \]
   \[ R^{29} \]
   \[ R^{30} \]
   \[ R^{27} \]
   \[ R^{23} \]
   \[ R^{24} \]
   \[ R^{25} \]

   Formula 2
wherein \(-\text{-----}\) is \(j\), \(s\), or \(i\), but consecutive \(-\text{-----}\) cannot be \\(\text{-----} \text{or} \triangle\);

the cyclohexane ring may be saturated or unsaturated with any degree of unsaturation provided that when a \(-\text{-----}\) attached to the ring is \(\triangle\) or \\
5 the ring carbon to which the \(-\text{-----}\) is attached is unsaturated;

\(X\) is \(-\text{O-}\) or \(-\text{O-O-}\);

\(Y\) is \(-\text{O-}\) or \(-\text{O-O-}\);

\(n\) is 0 or 1, \(m\) is 0 or 1, but \(n\) and \(m\) cannot both be 1 and neither \(n\) or \(m\) can be 1 if the \(-\text{-----}\) attached to the ring is \(\text{-----} \text{or} \triangle\)

10 \(R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}\) or \(R^{29}\) are each independently selected from \(H, OH, OOH, OC=OR, OR\); or an adjacent pair of \(R^{21}, R^{22}, R^{23}, R^{24}, R^{27}\)

or \(R^{28}\) may join to form an epoxide or \\
wherein any one of \(R^{22}, R^{23}, R^{27}, R^{28}\) or \(R^9\) may further be \(=O\), provided that \(=O\) is attached to an unsaturated carbon; \(o\) is 0 when the \(-\text{-----}\) to which \(R^{21}, R^{24}\) or \(R^{26}\) is attached is \(\text{-----} \text{or} \triangle\) and \(o\) is 1 when the \(-\text{-----}\) to which \(R^{21}, R^{24}\) or \(R^{26}\) is

15 attached is \(\text{-----} \text{or} \triangle\) and \(o\) is 1 when the \(-\text{-----}\) to which \(R^{21}, R^{24}\) or \(R^{26}\) is

\(R\) is a \(Ci\) to \(C_3\) alkyl;

wherein the compound contains at least two Oxygen atoms; and

(b) from 0 to 20% of at least one compound selected from the group consisting of a sesquiterpene, a sesquiterpene alcohol, a sesquiterpene epoxide, \(p\)-cymene, an oxygenated cyclohexane, an oxygenated cyclohexene, and a monoterpene, wherein the amount of any
monoterpenes in the fraction does not exceed 5% of the total composition, for use in the treatment or prophylaxis of cancer in a patient.

2. The composition of claim 1, comprising at least one compound of formula 1 selected from the group consisting of α-terpineol, β-terpineol, γ-terpineol terpinene-4-ol, menthol, thymol, carvacrol, carveol, perillyl alcohol, isopulegol, limonene-10-ol, and dihydrocarveol.

3. The composition of claim 1 or claim 2, characterized in that the at least one compound of formula 1 is terpinene-4-ol.

4. The composition of claim 3, comprising from about 40% to about 70% terpinene-4-ol.

5. The composition of claim 1, comprising at least two compounds of formula 1.

6. The composition of claim 5, characterized in that the compounds of formula 1 consist essentially of terpinene-4-ol and α-terpineol.

7. The composition of claim 5 comprising from about 40% to about 70% terpinene-4-ol and about 4% to about 15% terpinene-4-ol.

8. The composition of any one of claims 1 to 5, characterized in that the at least one compound of formula 2 is selected from the following compounds;
9. The composition of any one of claims 1 to 8, characterized in that the composition comprises at between about 10% to about 40%, preferably between about 15% to about 35%, preferably between about 20% to about 30% of at least one compound of formula 2.

10. The composition of claim 9, characterized in that the composition comprises at least two compounds of formula 2, and at least one compound has 2 oxygen atoms and at least one compound has three oxygen atoms, characterized in that the ratio of the at least one compound having two oxygen atoms to the at least one compound having three oxygen atoms is between about 1:1 to 5:1, preferably between about 1.5:1 to about 4:1, most preferably between about 2:1 to about 3:1.

11. The composition of claim 9, characterized in that the at least one compound of formula 2 comprises between about 1 to about 4%, preferably between about 2 to about 3% 2-hydroxy-1,4-cineole; between about 5% to about 15%, preferably between about 6% to about 12%, 1,4-dihydroxy-menth-2-en; between about 0.5% to about 5%, preferably between about 1% to about 4% 1,2-dihydroxy-menth-3-ene and between about 1 to about 10%, preferably between about 3% to about 6% 1,2,4-trihydroxy-menthane.
12. The composition of any one of claims 1 to 9 comprising form about 7% to about 15% p-cymene.

13. The composition of any one of claims 1 to 12 comprising at least one sesquiterpene.

14. The composition of claim 13, characterized in that the at least one sesquiterpene is selected from the group consisting of isoleadene, calamene, ledene, allo-aromadendrene, aromadendrene.

15. The composition of any one of claims 1 to 14 characterized in that the composition further comprises up to 5% of a compound of formula 3;

\[
\begin{align*}
\text{Formula 3} & \\
\text{wherein } & \\
\text{is } & \\
\text{or } & \\
\text{but consecutive cannot be } & \\
\text{Or } & \\
\text{R}^{31} & \text{and } \text{R}^{33} \text{ are each independently selected from H, OH, OOH, OC=OR, OR, } \text{R}^{31} \text{ may further be } =O \text{ provided that the } =O \text{ is not attached to an unsaturated carbon; } \text{R}^{32} \text{ is selected from the group consisting of CO, COOH, COH, COOR, COR; } \text{R}^{31} \text{ and } \text{R}^{32} \text{ may join to form a lactone; } \\
o & \text{is 0 when the } \text{to which } \text{R}^{10} \text{ is } & \\
\text{or } & \\
\text{and } & \\
o & \text{is 1 when the carbon to which } \text{R}^{33} \text{ is } & \\
\end{align*}
\]
R is a $C_1$ to $C_3$ alkyl.

16. The composition of any one of claims 1 to 15, formulated for oral administration.

17. The composition of claim 16, characterized in that the composition is administered in an amount of about 150mg to about 900mg preferably between about 150 to about 400mg and most preferably between about 150 to about 300 mg per day for a 70kg human.

18. The composition of any one of claims 1 to 16, characterized in that the cancer to be treated is selected from the group consisting of cervical cancer, non-small lung cell cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer.

19. The composition of claim 18, characterized in that the cancer is a primary cancer.

20. The composition of claim 19, characterized in that the composition is administered intraleisonally.

21. The composition of claim 18, characterized in that the cancer is metastatic.

22. The composition of any one of claims 1 to 17, characterized in that the cancer is leukaemia.

23. A method for the treatment of a cancer in a patient, the method comprising administering to the patient a therapeutically effective amount of composition comprising;

(a) 30% - 80% of at least one compound having the formula 1
wherein \( \text{----- is } \longrightarrow \text{ or } \longrightarrow \), but consecutive \( \text{----- cannot be } \longrightarrow \);

the cyclohexane ring may be saturated or unsaturated with any degree of unsaturation provided that when a \( \longrightarrow \) attached to the ring is \( = = \) the ring carbon to which the \( \text{----- is attached is unsaturated; } \)

one of \( R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 \) or \( R^9 \) is \( \text{OH} \), and each of the remaining \( R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 \) and \( R^9 \) is \( \text{H} \);

\( o \) is \( 0 \) when the \( \text{----- to which } R^1, R^4, R^5 \) or \( R^9 \) is attached is \( = \) and \( o \) is \( 1 \) when the \( \text{----- to which } R^1, R^4, R^5 \) or \( R^9 \) is \( \text{-----} \);

(b) \( 10\% \) to \( 40\% \) of at least one compound of formula 2

Formula 2

wherein \( \text{----- is } \longrightarrow, \longrightarrow \text{ or } \bigtriangleup \), but consecutive \( \text{----- cannot be } \longrightarrow \longrightarrow \text{ or } \bigtriangleup \);
the cydohexane ring may be saturated or unsaturated with any degree of unsaturation provided that when a attached to the ring is or the ring carbon to which the attached is unsaturated;

X is -O- or -0-0-;

Y is -O- or -O-O-;

n is 0 or 1, m is 0 or 1, but n and m cannot both be 1 and neither n or m can be 1 if the attached to the ring is or

R21, R22, R23, R24, R25, R26, R27, R28 or R29 are each independently selected from H, OH, OOH, OC=OR, OR; or an adjacent pair of R21, R22, R23, R24, R27 or R28 may join to form an epoxide or ; wherein any one of R22, R23, R27, R28 or R9 may further be =O, provided that =O is attached to an unsaturated carbon; o is 0 when the to which R21, R24 or R26 is attached is or and o is 1 when the to which R21, R24 or R26 is

R is a C1 to C3 alkyl;

wherein the compound contains at least two Oxygen atoms; and

(c) from 0 to 20% of at least one compound selected from the group consisting of a sesquiterpene, a sesquiterpene alcohol, a sesquiterpene epoxide, p-cymene, an oxygenated cydohexane, an oxygenated cyclohexene, and a monoterpene, wherein the amount of any monoterpenes in the fraction does not exceed 5% of the total composition.

24. The method of claim 23, wherein the at least one compound of formula 1 is selected from the group consisting of α-terpineol, β-terpineol, γ-terpineol
terpinene-4-ol, menthol, thymol, carvacrol, carveol, perillyl alcohol, isopulegol, limonene-10-ol, and dihydrocarveol.

25. The method of claim 23 or claim 24, wherein the at least one compound of formula 1 is terpinene-4-ol.

26. The method of claim 25 wherein the composition comprises from 40 % to 70% terpinene-4-ol.

27. The method of claim 23, wherein the composition comprises at least two compounds of formula 1.

28. The method of claim 23, wherein the compounds of formula 1 consist essentially of terpinene-4-ol and a-terpineol.

29. The method of claim 28 wherein the composition comprises between about 40 and about 70% terpinene-4-ol and about 4 to about 15% terpinene-4-ol.

30. The method of any one of claims 23 to 29, wherein the composition comprises at least one compound of formula 2 is selected from the following compounds;
31. The method of any one of claims 23 to 30, wherein the composition comprises at least one compound of formula 2 consists essentially of 2-hydroxy 1,4-cineole, dihydroxy-menth-2-ene, dihydroxy menth-3-ene, 4-trihydroxy - menthane and dihydroxy-menth-2-ene.

32. The method of any one of claims 23 to 31 wherein the composition comprises about 7 to about 15% p-cymene.

33. The method of any one of claims 23 to 32 wherein the composition comprises at least one sesquiterpene.

34. The method of claim 33, wherein the at least one sesquiterpene is selected from the group consisting of isoledene, calamene, ledene, allo-aromadendrene, aromadendrene

35. The method of any one of claims 23 to 34, wherein the composition further comprises up to 5% of a compound of formula 3;

Formula 3

wherein _____ is _____, or △, but consecutive ______ cannot

be _____ or △;
R\textsuperscript{31} and R\textsuperscript{33} are each independently selected from H, OH, OOH, OC=OR, OR, R\textsuperscript{1} may further be =O provided that the =0 is not attached to an unsaturated carbon; R\textsuperscript{32} is selected from the group consisting of CO, COOH, COH, COOR, COR; R\textsuperscript{1} and R\textsuperscript{32} may join to form a lactone; o is 0 when the to which R10 is or and o is 1 when the carbon to which R\textsuperscript{33} is and
R is a C\textsubscript{1} to C\textsubscript{3} alkyl.

36. The method of any one of claims 23 to 35, wherein the composition is formulated for oral administration.

37. The method of claim 36, wherein the composition is administered in an amount of about 150mg to about 900mg per day.

38. The method of any one of claims 23 to 37, wherein the cancer to be treated is selected from the group consisting of cervical cancer, non-small lung cell cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer.

39. The method of claim 38, wherein the cancer is primary.

40. The method of claim 39, wherein the composition is administered intralesionally.

41. The method of claim 38, wherein the cancer is metastatic.

42. The method of any one of claims 23 to 37, wherein the cancer is leukemia.

43. A method for minimizing the risk of a high risk cancer form developing a new or re-current cancer, the method comprising administering to the patient a therapeutically effective amount of a composition comprising:
(a) 30% - 80% of at least one compound having the formula 1
wherein ——— is ——— or ———, but consecutive ——— cannot be ———;

the cydohexane ring may be saturated or unsaturated with any degree of unsaturation provided that when a ——— attached to the ring is ——— the ring carbon to which the ——— is attached is unsaturated;

one of R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ or R₉ is OH, and each of the remaining R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ is H;

o is 0 when the ——— to which R₁, R₄, R₅ or R₉ is attached is ——— and o is 1 when the ——— to which R₁, R₄, R₅ or R₉ is ———;

(b) 10% to 40% of at least one compound of formula 2

wherein ——— is ———, ——— or △, but consecutive ——— cannot be ——— or △;
the cyclohexane ring may be saturated or unsaturated with any degree of unsaturation provided that when a \( \textbf{-} \) attached to the ring is \( \equiv \) or \( \xrightarrow{0} \) the ring carbon to which the \( \textbf{-} \) is attached is unsaturated;

\( X \) is -O- or -O-O-;

\( Y \) is -O- or -O-O-

\( n \) is 0 or 1, \( m \) is 0 or 1, but \( n \) and \( m \) cannot both be 1 and neither \( n \) or \( m \) can be 1 if the \( \textbf{-} \) attached to the ring is \( \equiv \) or \( \xrightarrow{0} \)

\( R^1, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28} \) or \( R^{29} \) are each independently selected from H, OH, OOH, OC=O, OR; or an adjacent pair of \( R^1, R^{22}, R^{23}, R^{24}, R^{27} \) or \( R^{28} \) may join to form an epoxide or \( \xrightarrow{0} \); wherein any one of \( R^{22}, R^{23}, R^{27}, R^{28} \) or \( R^9 \) may further be =O, provided that =O is attached to an unsaturated carbon; \( o \) is 0 when the \( \textbf{-} \) to which \( R^1, R^{24} \) or \( R^{26} \) is attached is \( \equiv \) or \( \xrightarrow{0} \) and \( o \) is 1 when the \( \textbf{-} \) to which \( R^1, R^{24} \) or \( R^{26} \) is \( \equiv \) and

\( R \) is a \( C_1 \) to \( C_3 \) alkyl;

wherein the compound contains at least two Oxygen atoms; and

(c) from 0 to 20% of at least one compound selected from the group consisting of a sesquiterpene, a sesquiterpene alcohol, a sesquiterpene epoxide, p-cymene, an oxygenated cyclohexane, an oxygenated cyclohexene, and a monoterpene, wherein the amount of any monoterpenes in the fraction does not exceed 5% of the total composition.

44. The method of claim 43, wherein the at least one compound of formula 1 is selected from the group consisting of \( \alpha \)-terpineol, \( \beta \)-terpineol, \( \gamma \)-terpineol
terpinene-4-ol, menthol, thymol, carvacrol, carveol, perillyl alcohol, isopulegol, limonene-10-ol, and dihydrocarveol.

45. The method of claim 43 or claim 44, wherein the at least one compound of formula 1 is terpinene-4-ol.

46. The method of claim 43 wherein the composition comprises from 40 % to 70% terpinene-4-ol.

47. The method of claim 43, wherein the composition comprises at least two compounds of formula 1.

48. The method of claim 47, wherein the compounds of formula 1 consist essentially of terpinene-4-ol and α-terpineol.

49. The method of claim 26 wherein the composition comprises between about 40 and about 70% terpinene-4-ol and about 4 to about 15% terpinene-4-ol.

50. The method of any one of claims 43 to 49, wherein the composition comprises at least one compound of formula 2 is selected from the following compounds;
51. The method of any one of claims 43 to 50, wherein the composition comprises at between about 10% to about 40%, preferably between about 15% to about 35%, preferably between about 20% to about 30% of at least one compound of formula 2.

52. The method of claim 51, wherein the composition comprises at least two compounds of formula 2, and at least one compound has 2 oxygen atoms and at least one compound has three oxygen atoms, wherein the ratio of the at least one compound having two oxygen atoms to the at least one compound having three oxygen atoms is between about 1:1 to 5:1, preferably between about 1.5:1 to about 4:1, most preferably between about 2:1 to about 3:1.

53. The method of claim 51, wherein the at least one compound of formula 2 comprises between about 1 to about 4%, preferably between about 2 to about 3% 2-hydroxy-1,4-cineole; between about 5% to about 15%, preferably between about 6% to about 12%, 1,4-dihydroxy-menth-2-en; between about 0.5% to about 5%, preferably between about 1% to about 4% 1,2-dihydroxy-menth-3-ene and between about 1 to about 10%, preferably between about 3% to about 6% 1,2,4-trihydroxy-menthane.

54. The method of any one of claims 43 to 53, wherein the composition comprises about 7 to about 15% p-cymene.

55. The method of any one of claims 43 to 54 wherein the composition comprises at least one sesquiterpene.

56. The method of claim 55, wherein the at least one sesquiterpene is selected from the group consisting of isoleadene, calamene, ledene, allo-aromadendrene, aromadendrene

57. The method of any one of claims 43 to 56, wherein the composition further comprises up to 5% of a compound of formula 3;
Formula 3

wherein \( \text{-----} \) is \( \text{-----} \), \( \text{-----} \) or \( \text{-----} \), but consecutive \( \text{-----} \)

\begin{align*}
10 & \text{ cannot be } \text{-----} \text{or } \text{-----} ; \\
15 & \text{ \( R^{31} \) and } \text{\( R^{33} \) are each independently selected from } \text{H, OH, OOH, OC=OR, OR, } \text{\( R^{31} \) may further be } =0 \text{ provided that the } =O \text{ is not attached to an unsaturated carbon; } R^{32} \text{ is selected form the group consisting of CO, COOH, COH, COOR, COR; } \text{\( R^{31} \) and } R^{32} \text{ may join to form a lactone;} \\
20 & \text{ o is 0 when the to which } R^{10} \text{ is or and o is 1 when the carbon to which } \text{\( R^{33} \) is and } \text{R is a } \text{C1 to C3 alkyl.} \\
25 & \text{58. The method of any one of claims 43 to 57, wherein the composition is formulated for oral administration.} \\
30 & \text{59. The method of claim 58, wherein the composition is administered in an amount of about 150mg to about 900mg per day, preferably between about 150 to about 400mg and most preferably between about 150 to about 300 mg per day for a 70kg human.}
\end{align*}
60. The method of any one of claims 43 to 59, wherein the cancer to be treated is selected from the group consisting of cervical cancer, non-small lung cell cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer and leukemia.

61. The method of any one of claims 43 to 60, further comprising genetically testing a patient to determine whether they are predisposed to a particular cancer.

62. The method of any one of claims 43 to 61, wherein the person at risk is a smoker.

63. Use of a composition comprising;

(a) 30% - 80% of at least one compound having the formula 1

![Chemical Structure](image)

wherein \( \text{---} \) is \( \text{---} \) or \( \text{---} \), but consecutive \( \text{---} \) cannot be \( \text{---} \);

the cyclohexane ring may be saturated or unsaturated with any degree of unsaturation provided that when a \( \text{---} \) attached to the ring is \( \text{---} \) the ring carbon to which the \( \text{---} \) is attached is unsaturated;

one of \( R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 \) or \( R^9 \) is \( \text{OH} \), and each of the remaining \( R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 \) and \( R^9 \) is \( \text{H} \);

\( o \) is 0 when the \( \text{---} \) to which \( R^1, R^4, R^5 \) or \( R^9 \) is attached is \( \text{---} \) and \( o \) is 1 when the \( \text{---} \) to which \( R^1, R^4, R^5 \) or \( R^9 \) is \( \text{---} \);

(b) 10% to 40% of at least one compound of formula 2
Formula 2

wherein \( i \) is 0 or \( \neq \), but consecutive \( i \) cannot be 0 or \( \neq \); the cyclohexane ring may be saturated or unsaturated with any degree of unsaturation provided that when a \( 0 = \) attached to the ring is 0 or \( \triangle \) the ring carbon to which the \( 0 = \) is attached is unsaturated;

\( X \) is -O- or -O-O-;

\( Y \) is -O- or -O-O-

\( n \) is 0 or 1, \( m \) is 0 or 1, but \( n \) and \( m \) cannot both be 1 and neither \( n \) or \( m \) can be 1 if the \( 0 = \) attached to the ring is 0 or \( \triangle \)

\( R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 \) or \( R^9 \) are each independently selected from H, OH, OOH, OC=OR, OR; or an adjacent pair of \( R^1, R^2, R^3, R^4, R^7 \) or \( R^8 \) may join to form an epoxide or \( \triangle \); wherein any one of \( R^2, R^3, R^7, R^8 \) or \( R^9 \) may further be \( =O \), provided that \( =O \) is attached to an unsaturated carbon; \( o \) is 0 when the \( 0 = \) to which \( R^1, R^4 \) or \( R^8 \) is
attached is = or and o is 1 when the \(-\) to which \(R^{21}, R^{24}\) or \(R^{26}\) is \(--\) and

\[ R \text{ is a } C_1 \text{ to } C_3 \text{ alkyl;} \]

wherein the compound contains at least two Oxygen atoms; and

from 0 to 20% of at least one compound selected from the group consisting of a sesquiterpene, a sesquiterpene alcohol, a sesquiterpene epoxide, \(p\)-cymene, an oxygenated cyclohexane, an oxygenated cyclohexene, and a monoterpene, wherein the amount of any monoterpenes in the fraction does not exceed 5% of the total composition, for minimizing the risk of a person at risk from cancer developing a new or recurrent cancer

64. The use of claim 63, wherein the composition comprises at least one compound of formula 1 selected from the group consisting of \(\alpha\)-terpineol, \(\beta\)-terpineol, \(\gamma\)-terpineol terpinene-4-ol, menthol, thymol, carvacrol, carveol, perillyl alcohol, isopulegol, limonene-10-ol, and dihydrocarveol.

65. The use of claim 63 or claim 64, wherein the at least one compound of formula 1 is terpinene-4-ol.

66. The use of claim 65, wherein the composition comprises from 40% to 70% terpinene-4-ol.

67. The use of claim 63, wherein the composition comprises at least two compounds of formula 1.

68. The use of claim 67, wherein the compounds of formula 1 consist essentially of terpinene-4-ol and \(\alpha\)-terpineol.

69. The use of claim 68 wherein the composition comprises between about 40 and about 70% terpinene-4-ol and about 4 to about 15% \(\alpha\)-terpineol.
70. The use of any one of claims 63 to 69, wherein the at least one compound of formula 2 is selected from the following compounds;
71. The use of any one of claims 63 to 70, characterized in that the composition comprises at between about 10% to about 40%, preferably between about 15% to about 35%, preferably between about 20% to about 30% of at least one compound of formula 2.

72. The use of claim 71, characterized in that the composition comprises at least two compounds of formula 2, and at least one compound has 2 oxygen atoms and at least one compound has three oxygen atoms, wherein the ratio of the at least one compound having two oxygen atoms to the at least one compound having three oxygen atoms is between about 1:1 to 5:1, preferably between about 1.5:1 to about 4:1, most preferably between about 2:1 to about 3:1.

73. The use of claim 71, characterized in that the at least one compound of formula 2 comprises between about 1 to about 4%, preferably between about 2 to about 3% 2-hydroxy-1,4-cineole; between about 5% to about 15%, preferably between about 6% to about 12%, 1,4-dihydroxy-menth-2-en; between about 0.5% to about 5%, preferably between about 1% to about 4% 1,2-dihydroxy-menth-3-ene and between about 1 to about 10%, preferably between about 3% to about 6% 1,2,4-trihydroxy-menthane.

74. The use of any one of claims 58 to 66 wherein the composition comprises about 7 to about 15% p-cymene.
75. The use of any one of claims 63 to 74 wherein the composition comprises at least one sesquiterpene.

76. The use of claim 75, wherein the at least one sesquiterpene is selected from the group consisting of isoleadene, calamene, ledene, allo-aromadendrene, aromadendrene

77. The use of any one of claims 63 to 76 wherein the composition further comprises up to 5% of a compound of formula 3;

![Chemical Structure](image)

**Formula 3**

wherein \(R^3\) is \(-\), \(=\) or \(\bigcirc\), but consecutive \(\bigcirc\) cannot be \(\bigcirc\) or \(\bigcirc\):

\(R^1\) and \(R^{33}\) are each independently selected from H, OH, OOH, OC=OR, OR, \(R^1\) may further be \(=O\) provided that the \(=O\) is not attached to an unsaturated carbon; \(R^{32}\) is selected from the group consisting of CO, COOH, COH, COOR, COR; \(R^1\) and \(R^{32}\) may join to form a lactone;

\(o\) is 0 when the \(-\) to which \(R^{10}\) is \(-\) or \(\bigcirc\) and \(o\) is 1 when the carbon to which \(R^{33}\) is \(-\) and

\(R\) is a C\(_1\) to C\(_3\) alkyl.
78. The use of any one of claims 63 to 77, wherein the composition is formulated for oral administration.

79. The use of claim 77, wherein the composition is administered in an amount of about 150mg to about 900mg per day, preferably between about 150 to about 400mg and most preferably between about 150 to about 300 mg per day for a 70kg human.

80. The use of any one of claims 63 to 79, wherein the cancer to be treated is selected from the group consisting of cervical cancer, non-small lung cell cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer or leukemia.
Cancer cell lines 24hrs

Fig. 1
## Developmental Therapeutics Program

### One Dose Mean Graph

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**Fig. 2**
Fig. 3

Fig. 4
Fig. 5
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

A61P37/02 A61P43/00 A61P35/00 A61P31/18 A61P25/32

According to International Patent Classification (IPC) onto both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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- X Further documents are listed in the continuation of Box C.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) on which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed
  "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  "A" document member of the same patent family

Date of the actual completion of the international search: 28 June 2012
Date of mailing of the international search report: 13/07/2012

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 JV Rijswijk
Tel. (+31-34) 340-2040,
Fax. (+31-34) 340-3016

Authorized officer:

Madal inska, K
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<td>wo 00/33858 AI (ECOSMART TECHNOLOGIES INC [US]; BESSETTE STEVEN M [US]; ENAN ESSAM E []) 15 June 2000 (2000-06-15) abstract; claims 1-15 ali-fa-terpeneol, carvacrol, carveol, menthol, terpinen-4-ol, thymol</td>
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