(54) Title: TURMERIC COMPOSITIONS AND METHODS FOR THE PREPARATION THEREOF

(57) Abstract: The invention relates to the use of a composition comprising ethanol, curcumin and a dissolved whole tumeric powder for the preparation of an alcoholic curcumin and turmeric liquid pharmaceutical composition for treating proliferative and other clinical disorders in a human patient the composition evidencing enhanced bioavailability vis-a-vis a comparable dosage of curcumin in dry powder form.
TURMERIC COMPOSITIONS AND METHODS FOR THE PREPARATION THEREOF

FIELD OF THE INVENTION

The present invention relates to the preparation of pharmaceutical compositions from extracts of medicinal plants and to pharmaceutical compositions prepared therefrom. More particularly, the invention relates to increasing the bioavailability of water-insoluble components of medicinal plants and especially of turmeric for medicinal purposes.

BACKGROUND OF THE INVENTION

The use of medicinal plants and products thereof is well known. Many spices, essences, leaves and flowers have been used for treating diseases around the world for several millennia. For example, peppermint is used for gastric ailments, garlic oil for earache and other disorders, St. John’s wort is used for relieving depression. There are numerous medicinal plants and many health shops sell dietary supplements made from one or more medicinal plants.

One of the major problems in preparing the medicaments/supplements for human consumption is that some of the active ingredients of the plants are relatively water insoluble. The active ingredients which are supplied in an oral form must be absorbed from the human digestive tract in order to become usable by a human subject. In the case of turmeric it was found that turmeric powder in the form of most commercially available capsules is poorly absorbed through the intestine and therefore there is a need to provide curcumin and turmeric in a form that will have higher bioavailability. Thus, there is a need to provide the active ingredients in a form that can be biologically absorbed by the body, that is, in a bioavailable form.

The issue of safety of curcumin and turmeric to humans has been discussed in quite a few recent publications and it has been found to be non-toxic. In this context one can see a review by S. Bengmark,
"Curcumin, an atoxic antioxidant and natural NFkappaB, cyclooxygenase-2, lipooxygenase and inducible nitric oxide synthase inhibitor: a shield against acute and chronic diseases", JPEN J Parenter Enteral Nutr. 2006 Jan-Feb; 30(1):45-51. In this review a literature search (PubMed) showed 1500 papers dealing with curcumin. The conclusion of the review as quoted from the abstract reads: "RESULTS: Curcumin a component of turmeric, has been shown to be non-toxic..."

Curcumin (diferuloylmethane) is a polyphenol derived from the plant Curcuma longa, commonly called turmeric. Extensive research over the last 50 years has indicated that this polyphenol can both prevent and treat cancer and a number of other diseases and clinical conditions.

There are several molecular targets that were shown to be regulated by curcumin, which explain, at least in part, some of its anti-cancer properties.

In mammalian cancer, a number of alterations to normal cell function occur and there are several opportunities to inhibit, slow down or even reverse the process. A chemo-preventive agent can either prevent the occurrence of cell damage, or can counteract any damage that has already transpired.

Curcumin has been shown, by a number of investigators, to be a chemo-preventive agent in varying ways.

Curcumin was shown to suppress the proliferation of a wide variety of tumor cells, and down-regulate transcription factors such as NF-kappa B, AP-1, Egr-1, beta-catechin and PPAR-gamma. Curcumin was also shown to down-regulate the expression of enzymes, such as COX2, 5-LOX, iNOS and hemeoxygenase-1, as well as down-regulating MMP-9, uPA, TNF, chemokines, cell surface adhesion molecules and cyclin D1. Curcumin also down-regulates growth factor receptors (such as EGFR and HER2), and inhibits the activity of c-Jun N-terminal kinase, protein tyrosine kinases and protein serine/threonine kinases. (Aggarwal, B. B. et al., Curcumin Derived from Turmeric (Curcuma longa): A Spice For All Seasons, in: Phytopharmaceuticals in Cancer Chemoprevention, pp. 349-387, CRC 2005.)
Curcumin has been described as a potent antioxidant and anti-inflammatory agent. Evidence has also been presented to suggest that curcumin can suppress tumor initiation, promotion and metastasis (Maheshwari, R. K. et al., Multiple Biological Activities Of Curcumin: A Short Review, Life Sciences 78, 2081-2087, Elsevier 2006.).

Pharmacologically, curcumin has been found to be safe. Human clinical trials indicated no dose-limiting toxicity when administered at doses of up to 10 g/day (Cheng A L et al., Phase I Chemoprevention Clinical Trial Of Curcumin. Proc. Am. Soc. Clin. Oncol., 17:558a 1998), contrary to the findings of US 6,284,224 (supra). All these studies suggest that curcumin has enormous potential in the prevention and therapy of cancer and as an anti-inflammatory agent.

Curcumin has been shown to inhibit a wide range of clinical conditions, such as, but not limited to, inhibition of tumor growth and metastasis; inhibition of androgen receptors and AR-related cofactors, inhibition of atherosclerosis and myocardial infarction, inhibition of platelet aggregation; inhibition of proliferation of vascular smooth muscle cells, inhibition of LDL oxidation and was also reported to lower serum cholesterol levels.

Other beneficial effects of curcumin that were studied are: suppression of diabetes; stimulation of muscle regeneration; enhancement of wound healing; suppression of arthritis; reduction of gallstone formation; modulation of MS; blocking the replication of HIV, reducing the effects of Alzheimer's disease; protecting against cataract formation; protecting from the effects of alcohol-induced liver injury; protecting from inflammatory bowel disease; and protecting against various forms of stress.

Despite the fact that curcumin has been shown to exhibit a wide range of beneficial uses, such as for the treatment of inflammatory conditions and other diseases, it has not been used widely and there are only several clinical trials to date. Most of the studies establishing curcumin's therapeutic efficacy were carried out on animals, or in vitro on tissue cultures.
One major limitation to the application of curcumin to date is that it has low bioavailability in humans. Curcumin administered orally to humans, was shown to be poorly absorbed by the intestine (Ravindranath and Chandrasekhara, Absorption and Tissue Distribution Of Curcumin In Rats, Toxicology 16, 259-165, 1980; Ravindranath V. et al., In vitro Studies On The Intestinal Absorption Of Curcumin In Rats, Toxicology 20, 251-257, 1981; Ravindranath et al. Metabolism of Curcumin-Studies with [3H] Curcumin, Toxicology 22, 337-344, 1982).

Oral consumption of curcumin in rats resulted in approximately 75% of the curcumin being excreted in the feces and only traces appearing in the urine, suggesting poor absorption of curcumin from the intestine (Holder et al 1978).

In a clinical research study on humans, it was shown that even after an oral dose of 2 gr. of curcumin in a capsule form, serum levels of curcumin were undetectable or very low. Neither curcumin nor its metabolites were found in the plasma or urine. The levels of curcumin detected in the feces, however were high.

Due to the large amounts of curcumin in the form of turmeric powder that were administered, some patients developed diarrhea or experienced nausea and had to withdraw from the experiment. (Sharma, R A et al. 2001, Clinical Cancer Research Vol. 7, 1894-1900).

Increase in bioavailability of curcumin was shown in a study that combined Terikatu with curcumin. Terikatu consists of equal parts of black pepper, long pepper and ginger (1:1:1), and is used in Ayurveda (an ancient Indian healing system based on body and soul, which system is now used by many natural holistic practitioners in the west). Terikatu (which has an enhancing effect on food absorption) has a bioavailability enhancing effect (Shoba et al. Planta Med., 64(4), 353-356, 1998).

The anti-cancer activity of curcumin in humans is effective in colon cancer patients where the curcumin acts directly on the cancer cells in the colon. Therefore, colon cancer patients in the early stages of the disease could benefit from the anti-cancer activity of curcumin in the form of powder.
However, since absorption by the blood is very poor, curcumin cannot work on metastases or on cancer in other organs.

There is thus a need to provide anti-cancer medicaments for human use which demonstrate both high bioavailability and low cytotoxicity.

5 SUMMARY OF THE INVENTION

The present invention is directed to the use of a composition comprising ethanol, curcumin and a dissolved whole tumeric powder for the preparation of an alcoholic curcumin and turmeric liquid pharmaceutical composition for treating proliferative and other clinical disorders in a human patient said composition evidencing enhanced bioavailability vis-à-vis a comparable dosage of curcumin in dry powder form.

Thus, the present invention is directed to a liquid pharmaceutical composition comprising ethanol, curcumin and a dissolved whole tumeric powder as described herein, wherein the composition is dissolved in water and adapted to be absorbed from the intestine into the bloodstream with high bioavailability.

The present invention is directed to methods and products for treating proliferative and other disorders in human patients. In particular, there are described methods for preparing ethanolic curcumin and turmeric liquid compositions for treating clinical disorders following absorption thereof in the blood stream.

Thus, it has now been surprisingly discovered that by using an alcohol and preferably ethanol as an extractant or carrier for curcumin in combination with dissolved whole tumeric powder it is possible to produce a liquid composition suitable for oral administration which demonstrates high bioavailability heretofore not achieved with any other form of delivery and coupled with no human toxicity.

Thus the present invention provides an alcoholic curcumin and turmeric liquid composition for treating a wide variety of clinical disorders including proliferative disorders in human patients.

The composition preferably comprises ethanol, dissolved whole turmeric powder and curcumin 95%-98% powder. The extract of the whole turmeric powder provides, in addition to curcuminoides, volatile compounds
and sesquiterpenoids. These compounds together with the curcuminoids seem to have a synergistic effect that enhances the bio-absorption of the curcumin and turmeric extract through the intestine to the bloodstream.

As is known, curcumin is the active component of Turmeric, and makes up 2-5% of the spice turmeric. The relationship between turmeric and curcumin is summarized in the review: "Turmeric and curcumin: biological actions and medicinal applications" by I. Chatto Padhyay et al., current science, vol 187. no.1, 10 July 2004. According to this review, there are three curcuminoids in turmeric. The main curcuminoid is curcumin or diferuloylmethane, consists 77% of the "curcumin powder" The other two curcuminoids are: demethoxycurcumin (17%) and bis-demethoxycurcumin (3%). Thus, the turmeric ethanolic extracts of the present invention contain these three curcuminoids that are generally referred to as "curcumin"

In preferred embodiments of the present invention said composition further comprises at least one alcohol-extracted component of propolis.

In some preferred embodiments of the present invention said composition further comprises at least one alcohol-extracted component of ginger.

In other preferred embodiments of the present invention said composition further comprises at least one alcohol-extracted component of Lippia citriodora

In yet another preferred embodiment of the present invention said composition further comprises glycerin.

The compositions prepared according to the present invention are effective for treating proliferative disorders selected from the group consisting of a myeloma, multiple myeloma, breast cancer, neuroblastoma, colorectal cancer, prostate cancer, pancreatic cancer, a malignant tumor, brain stem glioma, as well as other clinical disorders such as Alzheimer's disease, Crohn's disease, high cholesterol levels, Parkinson's disease, constipation and more.

As demonstrated in the examples hereinafter, it has been found that the composition is mixed in water and thus is adapted to be absorbed from
the intestine into the bloodstream of the human patient with a high bioavailability.

Preferably said composition is prepared using an alcoholic extract of whole tumeric powder.

Also, preferably said composition is prepared using an alcoholic extract of curcumin.

Also, preferably said composition is administered to patients by mixing 2ml-5ml of the extract in 200ml water.

In preferred embodiments of the present invention, said composition further comprises a pharmaceutically acceptable carrier.

In a most preferred embodiment of the present invention said curcumin comprises a plurality of curcuminoids.

As stated above, in some preferred embodiments, the prepared composition preferably also incorporates an alcohol extracted component of ginger.

Botanically, ginger is a member of the same family as turmeric, the Zingiberaceae family. Ginger is the rhizome (underground stem) of the plant Zingiber officinale. The extract of ginger is rich in gingerols and shogaols, which exhibit antioxidant, anti-inflammatory, anti-fungal anti-mycobacterial and anti-carcinogenic properties. Ginger also assists in the absorption of curcumin through the digestive system.

According to some other embodiments of the present invention, the composition further comprises at least one alcohol-extracted component of aloysia (Lippia citriodora). Recent research shows that aloysia contains an anti-cancer agent called citral ("Citral is a new inducer of caspase-3 in tumor cell lines", by N. Dudai et al. in Planta Med 2005;71;484-488)

Another aspect of the present invention provides for the use of a composition comprising a mixture of an alcohol and oil, curcumin and a dissolved whole tumeric powder for the preparation of a curcumin and tumeric liquid pharmaceutical composition for treating proliferative and other clinical disorders in a human patient said composition evidencing enhanced bioavailability vis-à-vis a comparable dosage of curcumin in dry powder form.
It has been found that this composition is adapted to be absorbed into the lymphatic system. In preferred embodiments of the present invention, said oil is canola oil. There is thus provided according to some embodiments of the present invention, an oil and alcohol extract composition of curcumin and dissolved whole turmeric powder for treating a proliferative disorder in a human patient, the composition comprising: at least one oil; and at least one ethanolic extracted component of whole turmeric powder and ethanolic extracted curcumin.

The alcoholic turmeric and curcumin liquid composition of the present invention is effective for the treatment of a proliferative disorder selected from the group consisting of a myeloma, multiple myeloma, breast cancer, neuroblastoma, colorectal cancer, prostate cancer, pancreatic cancer, a malignant tumor, brain stem glioma and other diseases and health disorders.

Similarly, the oil extract composition of turmeric and curcumin of the present invention is effective for the treatment of a proliferative disorder selected from the group consisting of a myeloma, multiple myeloma, breast cancer, neuroblastoma, colorectal cancer, prostate cancer, pancreatic cancer, a malignant tumor, brain stem glioma, and other diseases and health disorders.

Some further embodiments of the present invention are directed to an oral dosage form comprising ethanol, curcumin and a dissolved whole turmeric powder and a pharmaceutically acceptable carrier mixed in water.

In another aspect of the present invention there is provided a method for preparing a medicament for treating a proliferative and other disorders in a human patient, the method comprising:

(a) extracting at least one plant powder comprising whole turmeric in heated ethanol; and

(b) extracting curcumin in heated ethanol; and

(c) combining said extracts to form an ethanolic curcumin and turmeric composition.
In preferred embodiments of the present invention, said method further comprises extracting at least one further plant powder selected from the group consisting of propolis powder, ginger and Aloysia (Lippia citriodora).

Preferably the ethanolic curcumin and turmeric composition comprises curcuminoids: selected from the group consisting of curcumin (diferuloylmethane), demethoxycurcumin and bis-demethoxycurcumin, as well as volatile and other compounds of turmeric.

In preferred embodiments of the present invention the extracting steps comprise heating the ethanol to about its boiling point.

In especially preferred embodiments of the present invention the extracting steps further comprise cooling the ethanolic turmeric and curcumin extracts to about 60°C.

Preferably the extracting steps further comprise heating the ethanolic curcumin and turmeric extracts to about its boiling point after the cooling step.

In some cases, the at least one plant powder further comprises at least one of propolis powder, ginger root and aloysia.

According to some embodiments, the ethanolic turmeric and curcumin extract comprises curcumin (diferuloylmethane) 95-98%, or more precisely a mixture of curcuminoids including: curcumin, demethoxycurcumin and bis-demethoxycurcumin.

The method, in some embodiments further comprises filtering the ethanolic curcumin and turmeric extract to remove undissolved solids.

In some cases, the method further comprises mixing glycerin with ethanol in equal parts and preheating the mixture to 100°C.

In some other cases, curcumin and turmeric are extracted with canola oil.

In some cases, the method further comprises mixing glycerin with the ethanolic curcumin and turmeric extract.

According to some examples, the glycerin is preheated to around 80°C.
In some embodiments, the method further comprises mixing heated glycerin with ethanol and with turmeric powder and curcumin powder.

The use of ethanol, curcumin and a dissolved whole turmeric powder according to some embodiments of the present invention, is for the manufacture of a pharmaceutical liquid composition for the treatment of a wide range of clinical disorders in humans, including proliferative disorders selected from the group consisting of myeloma, multiple myeloma, breast cancer, neuroblastoma, colorectal cancer, prostate cancer, pancreatic cancer, a malignant tumor, brain stem glioma, and other diseases and health disorders.

Some embodiments of the present invention are directed to a method for treating a proliferative disorder in a human patient comprising administering to said patient a pharmaceutically effective amount of a liquid pharmaceutical composition comprising ethanol, curcumin and a dissolved whole turmeric powder as described herein.

U.S. Pat. No. 6,056,971 to Goldman, discloses a method for enhancing the dissolution properties of certain relatively insoluble dietary supplements. The method includes the steps of providing at least one relatively water insoluble dietary supplement, solubilizing the dietary supplement with a solubilizer, and incorporating an edible polyhydric alcohol into the solubilized dietary supplement to provide a liquid dietary supplement composition that can be dissolved in an aqueous system.

Suitable dietary supplements or therapeutic agents include, for example, micronutrients such as vitamins, minerals, and other nutritional co-factors. Exemplary agents include, but are not limited to, Coenzyme Q-10 (Ubiquinone), Turmeric Extract (Curcuminoids), Beta Carotene, Mixed Carotenoids Complex, Lutein, Lycopene, Tocotrienols, Tocopherols (Vitamin E), Saw Palmetto Lipid Extract, Exhinacea Extract, Hawthorne Berry Extract, Ginseng Extract, Lipoic Acid (Thiotic Acid), Ascorbyl Palmitate, Kava Extract, St. John's Wort (Hypericum), Extract of Quercetin, Dihydroepiandrosterone, Indol-3-carbinol, and mixtures thereof.

While said patent mentions the possible use of turmeric as such a dietary supplement, even though all the claims are limited to enhancing the
dissolution and bioavailability properties of coenzyme Q\textsubscript{10} and dietary supplements containing the same, it is to be noted that said patent specifically requires the use of a solubilizer and a polyhydric alcohol such as propylene glycol, glycerol and mixtures thereof, and does not teach or suggest the use of ethanol as an extractant or carrier for turmeric.

U.S. Pat. No. 6,284,224, to Kapadia, et al., discloses the inhibitory effect of synthetic and natural colorants on carcinogenesis in mice. A series of plant extracts was evaluated for inhibitory effects on carcinogenesis. The \textit{in vitro} inhibitory effects of beet root extract and of grape extract on Epstein-Barr virus early antigen induction in Raji cells exposed to the tumor promoter TPA were assayed, and found to show significant anti-tumor promoting activity. In fact, the inhibitory activity of beet root extract was found to be greater than that shown by extracts of red bell peppers, red onion skin, paprika, and cranberries. \textit{In vivo} studies of carcinogenesis inhibition by beet root extract were then performed. When beet root extract was given orally to mice, formation of skin tumors promoted by topical application of TPA or by exposure to UV radiation was significantly reduced. Also, beet root extract given orally reduced the incidence of glycerol-promoted pulmonary tumor formation.

Research was also performed on natural food colorants extract from turmeric, annatto seeds, and paprika. These colorants are commercially available in a variety of formulations in aqueous, vegetable oil, or propylene glycol vehicles. These vehicles may also contain emulsifiers and/or dispersants such as polysorbate 80 and lecithin. Recent studies have reported that colorants derived from turmeric, annatto, and paprika inhibit carcinogenesis. In the work described herein, the anti-tumor promoting activity of over thirty natural colorant formulations was investigated. Many of these formulations were found to exhibit significant \textit{in vitro} inhibition of EBV-EA activation in Raji cells. However, many of these formulations exhibited cytotoxicity, suggesting that use of these compositions to inhibit tumor formation may pose hazards to human health. Fortunately, some compositions which inhibited EBV-EA activation without exhibiting cytotoxicity were identified. The most effective of these compositions were;
a) a mixture of natural extractives of annatto seeds and turmeric with polysorbate 80, potassium hydroxide, and propylene glycol; and b) a natural extractive of paprika in vegetable oil. In vivo studies showed that oral feeding of paprika and annatto extracts act to inhibit TPA-induced skin tumor formation. They were also found to be effective anti-inflammatory agents.

It is to be noted however, that in said patent, turmeric is described as being provided with vegetable oil and this patent also does not teach or suggest the use of ethanol as an extractant or carrier for turmeric.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

The following description discloses curcumin and turmeric extract medicaments for human use, which demonstrate high bioavailability, high concentration of curcuminoids and low human toxicity, Curcuminoids are the active components of turmeric, and make up 2-5% of the turmeric. In the present invention we extract pure curcuminoids powder, commonly referred to as "curcumin" (95%-98%), together with turmeric powder, both to form a saturated solution. Thus we get a liquid extract with high concentration of curcuminoids, together with the volatile and other compounds of turmeric.

The medicaments of the present invention were prepared according to the following methodologies:

RAW MATERIALS:

Powders

A powder of curcuminoids referred to as Curcumin 95%-98% (in the form of a yellow powder obtained from turmeric) and turmeric (a powder of the rhizomes of Curcuma longa), and propolis powder were all obtained commercially from Alalim, Zippori, Israel.

Solvents

Ethanol 95% B.P., and glycerin B.P. Solvents were obtained commercially from Sigma Chemicals Israel.

Extracts

Ginger extract (called herein ginger tincture) as a 70% ethanolic extract from ginger root with the concentration of the ginger extract being 1:4).
Lippia citriodora (=Aloysia citriodora) tincture (a 70% ethanolic extract of Lippia citriodora) The tinctures were obtained from: A.M.B. Beth Shemesh.

Preparations Of Liquid Curcumin and Turmeric Extract

Example 1:

Liquid Alcoholic Extract of Curcumin and Turmeric

The starting materials were 20 gram of pure curcumin powder (95%-98%), 100 gram of turmeric powder and 1 liter of ethanol.

Mode of Preparation

a) A mixture of curcumin powder with turmeric powder was dissolved in one liter of ethanol, for example by heating the mixture in a receptacle, such as in a two liter Ehrlenmeyer flask placed in a boiling water bath, until the mixture started to boil at around 77°C.

b) The mixture was then mixed by a magnetic stirrer, while cooling down to 60°C in ambient air for around ten minutes.

c) Thereafter, the mixture was heated again to around its boiling point (observed visually) in a hot water bath while mixing.

d) In the next step, the mixture was cooled down in ambient air. It was seen that the excess of undissolved curcumin and turmeric particles settled at the bottom of the flask.

e) The mixture and particles were filtered using a vacuum filter and Whatman filter paper (Whatman Filter Paper No. 2) such that a clear extract solution passed through the filter paper and the undissolved particles remained on the filter paper. A clear dark yellow-red ethanolic turmeric extract solution was collected.

The taste of the mixture may be adjusted by adding to the final composition 1%-2% of an ethanolic extract of lemon or orange.

Example 2:

Liquid Curcumin and Turmeric Extract With Glycerin

The starting materials were 20 gram of pure curcumin powder (95%-98%), 100 gram of turmeric powder, 500 ml ethanol and 500 ml glycerin.

Mode of preparation:

a) 500 ml of glycerin was heated to 80°C, such as in a two liter Ehrlenmeyer flask placed in a boiling water bath.
b) 500 ml of ethanol 95% was added to the hot glycerin and further heated to 88°C.

c) The turmeric powder was mixed with the curcumin powder and added to the glycerin-ethanol hot mixture with constant stirring.

d) Thereafter the mixture was heated again to around its boiling point in a water bath while mixing.

e) The mixture was cooled down in ambient air. It was seen that the excess of undissolved curcumin and turmeric particles settled at the bottom of the flask, a procedure that may have taken 12 hours.

f) The mixture and particles were filtered using a vacuum filter and Whatman filter paper, such that a clear extract solution was collected.

Example 3:
Liquid Curcumin and Turmeric Extract With Glycerin, Ginger Tincture and Lemon Verbena Tincture

The starting materials were 20 gram of pure curcumin powder (95%-98%), 100 gram of turmeric powder, 500 ml ethanol and 500 ml glycerin, 55 ml ginger tincture, 25 ml lemon verbena tincture.

Mode of preparation:

a) 500 ml of ethanol 95% was heated to 70°C, such as in a two liter Erlenmeyer flask placed in a boiling water bath.

b) The mixture of pure curcumin and turmeric powders were mixed in the hot ethanol using a magnetic stirrer.

c) The mixture was cooled down in ambient air. It was seen that the excess of undissolved curcumin and turmeric particles settled at the bottom of the flask, a procedure that may have taken 2 hours.

d) The mixture and particles were filtered using a vacuum filter and Whatman filter paper, such that a clear extract solution was collected.

e) circa 400-450 ml of clear yellow-red dark curcumin and turmeric extract solution was collected.

f) Equal amount of glycerin (circa 400-450 ml) was heated to 80°C.

g) The clear ethanolic extract of curcumin and turmeric was added to the hot glycerin and heated further to 70°C while mixing.
h) 55 ml ginger tincture (4%-6%), and 25 ml ethanolic extract of Lippia citriodora (=Aloysia citriodora) (1%-3%) tincture were added.
i) The mixture of step g) and step h) were mixed well by means of a magnetic stirrer.

Example 4

Liquid Oil Extraction of Curcumin and Turmeric

The importance of the oil extract of turmeric is that it enables direct absorption into the lymphatic system. The ethanolic extract is absorbed by the blood from the intestine.

The lymphatic system plays an important role in cancer conditions and thus the direct absorption to the lymphatic system is of great importance.

Raw materials:

- Powder of turmeric
- Powder of Curcumin (=curcuminoids)
- Canola oil
- Lecithin (liquid)
- Ethanol 95%
- Ginger extract (70% ethanolic extract)

Mode of Preparation

a) 400ml of canola oil was mixed with 8-10 ml liquid lecithin and heated to 80°C in a 2000ml Erlenmeyer flask. 50 gram turmeric powder and 10 grams curcumin powder were added and mixed with a magnetic stirrer, while keeping the temperature on 80°C for 20 minutes to form an oil curcumin and turmeric extract.

b) The oil curcumin and turmeric extract was cooled to room temperature.
c) The cooled oil curcumin and turmeric extract was filtered employing a vacuum filter (Whatman no. 2 filter paper) to form a clear yellow oil fraction.
d) To 300 ml of curcumin and turmeric clear oil extract, we added 700 ml of the liquid alcoholic extract of curcumin and turmeric (Example 1),
e) 50 ml of ginger extract was added and mixed well

Example 5:

Ethanolic extract of Curcumin and Turmeric and Propolis
The starting materials were 100 g of turmeric powder, 20 g. of
curcumin powder, 50 g propolis powder and 1000 ml ethanol 95%

Mode of preparation:
A clear dark yellow-red ethanolic curcumin and turmeric extract
solution was prepared as in steps a)-e) of Example 1.
f) 50 g of propolis powder was added to the curcumin and turmeric extract
solution and was mixed well for 30 minutes to allow the propolis powder to
dissolve. It was noted that some of the propolis powder did not dissolve.
g) The undissolved solids were allowed to settle.

h) Thereafter, the solution and solids were filtered using a vacuum filter and
Whatman filter paper (Whatman filter paper no. 2) such that a clear extract
solution passed through the filter paper and the undissolved particles
remained on the filter paper. A clear brownish ethanolic curcumin, turmeric
and propolis extract solution was collected.

It should be understood that this methodology is not meant to be
limiting. For example, the propolis powder could be added to the ethanol in
step a), for example, and then steps f)-h) would not be performed.

Example 6:
Glycerin extract of Curcumin, Turmeric and Propolis

The starting materials were 50 g of turmeric powder, 10 g of
curcumin powder, 50 g propolis powder 500 ml ethanol 95% and 600 ml
glycerin.

Mode of preparation:
a) The turmeric powder mixed with the curcumin powder were dissolved in
500 ml of ethanol, for example by heating the mixture in a receptacle, such
as a two liter Erlenmeyer flask placed in a boiling water bath for a few
minutes, until the mixture started to boil at around 77°C.
Steps b)-e) were performed as in Example 1 to form around 300-400 ml of
clear dark yellow-red ethanolic curcumin and turmeric extract solution.
f) 50 g of propolis powder was added to the turmeric extract solution and
was mixed well for 30 minutes to allow the propolis powder to dissolve. It
was noted that some of the propolis powder did not dissolve.
g) The undissolved solids were allowed to settle.
h) Thereafter, the solution and solids were filtered using a vacuum filter and Whatman filter paper (Whatman Filter Paper No. 2 such that a clear extract solution passed through the filter paper and the undissolved particles remained on the filter paper. A clear brownish ethanolic turmeric propolis extract solution was collected.

i) 600 ml of glycerin was heated to 80 °C such as in a two liter Ehrlenmeyer flask placed in a boiling water bath.

j) The hot glycerin of step i) was added to 400 ml of the clear extract of step h) and was mixed well by means of a magnetic stirrer.

**Examples 7, 8, 9, 10**

Examples 1, 2 5 and 6 were repeated as described hereinabove, but in the last step 45-65 ml of an ethanolic extract of ginger root concentrated at 1:4 (A.M.B. Beth Shemesh, Israel) was added to the final clear extract, such that in example 7) a curcumin, turmeric and ginger ethanolic extract solution was formed; in example 8) a curcumin, turmeric and ginger glycerin-ethanolic extract solution was formed; in example 9) a turmeric-propolis-ginger ethanolic extract solution was formed; and in example 10) a turmeric-propolis-ginger glycerin ethanolic extract solution was formed.

The final relation of ginger extract and the lemony extract of Lippia citriodora added to the examples given is the following: 45 ml- 65 ml of the ethanolic extract of ginger is added to 920 ml-940 ml of curcumin and turmeric extract (circa 4% - 6%), to form 1000 ml of final extract.

Adding a lemon taste is performed by: 20 ml – 30 ml ethanolic extract of Lippia citriodora (=Aloysia citriodora) (circa 1% - 3%) were added to form 1000 ml of final curcumin and turmeric extract.

**Applications of the ethanolic turmeric extracts in treating human patients**

This invention describes the use of the ethanolic curcumin and turmeric extracts prepared as described hereinabove in preliminary clinical trials performed over a three year period. Many of the patients were prescribed to use the curcumin and turmeric extracts by the Department of Immunotherapy and Cancer of the Hadassah Medical Center, Ein-Karem, Jerusalem, Israel.
The extracts of curcumin and turmeric were administered to the patients mixed in water. More precisely: 2ml-5ml of a given extract was mixed in 200ml water.

**CASE STUDIES**

**Case 1**

The most significant case was a male, age 60, diagnosed four years ago with a malignant tumor in the brain stem (brain stem glioma).

Four years ago, the patient underwent MRI of the brain to detect and measure the tumor's size and position. The patient reported problems in one leg that became weak and limited his walking ability. The pressure on the brain also caused some personality changes and the person who previously had a calm personality became violent with his closest relatives.

The tumor could not be removed surgically as it grew in an area where surgery might have destroyed essential structures of the brain. Therefore radiation therapy was employed for one month, 5 times a week, for a total of 20 radiation sessions.

The prognosis for life expectancy was that of about 3-6 months. Medical statistics show that only about 25% of people with brain stem glioma survive for more than a year and more likely if they are under age 45.

For the last 45 months, the patient was treated with the brownish ethanolic curcumin-turmeric-propolis extract of Example 5 (4 ml in a glass of water three times a day on an empty stomach).

The patient's MRI's during the last 45 months showed a considerable shrinkage of the tumor. Many of the faculties of the patient were restored although he still exhibits fatigue.

This case is very significant as the patient did not receive any other conventional medicine or any other treatment except the liquid curcumin, turmeric and propolis extract of Example 5.

**Case 2**

A male aged 60 who suffers from multiple myeloma received the curcumin-turmeric-propolis extract solution of Example 5 (4ml in a glass of water 3 times a day, on an empty stomach). The patient was given the
curcumin-turmeric-propolis extract for 24 months. During this period the patient had undergone a bone marrow transplant. The transplant had no effect on the disease. The patient kept taking the turmeric extract (Example 1) for additional 12 months. During this period the patient's blood tests showed significant improvement as the abnormal antibodies, the Bence-Jones proteins were negative (the Bence-Jones proteins are the markers for multiple myeloma). At this point the patient stopped taking the turmeric extract and within a few months there was a relapse and the multiple myeloma symptoms returned.

After that the patient was prescribed to take Velcade treatment. During this time the patient did not take the turmeric extract. But as the Velcade treatment failed, the patient started taking the turmeric extract (example 1) 2ml in water X 3 times a day. A few months later the patient was also prescribed Revlimid. As of today the patient's blood tests showed that the Bence-Jones proteins are negative and he keeps taking the curcumin-turmeric extract (example 3) 1 teaspoon in a glass of water, 3-4 times a day.

**Case 3**

A female, age 70, was diagnosed with colorectal cancer. The cancer had spread with metastases to the liver. After chemotherapy, the patient was treated with Avestin (bevacizumab), and liquid curcumin and turmeric extract (Example 1). Avestin is a humanized monoclonal antibody that stops tumor growth by preventing the formation of new blood vessels. It inhibits the function of a natural protein called vascular endothelial growth factor that stimulates new blood vessel formation.

The liquid curcumin and turmeric extract was administered at a dose of 2ml in a glass of water 3 times a day, on an empty stomach. After two months of liquid curcumin and turmeric extract treatment there was a significant retreat of the metastases and indications of improvement.

Avestin has shown some promising results in inducing tumor regression patients with solid colon tumors. But treatment with Avestin is not risk free and its efficacy is limited. The medical staff of the given case
attributed the retreat of the metastases to the combined action of Avestin and the liquid curcumin and turmeric extract.

Case 4

A male, age 74, was diagnosed with early stages of multiple myeloma. The only treatment administered to him was the curcumin and turmeric extract of Example 1 (2ml in a glass of water 3 times a day, on an empty stomach). According to the patient's testimony, after two months of liquid curcumin and turmeric extract treatment there was a significant retreat of the disease.

Case 5

A female, age 60, was diagnosed with breast cancer. The patient underwent chemotherapy and after the chemotherapy received the curcumin and turmeric extract solution of Example 1 (2ml in a glass of water 3 times a day, on an empty stomach). The patient reported good recovery from chemotherapy and basically feels well. The use of the curcumin and turmeric extract appears to enable her to lead a relatively normal life. The curcumin and turmeric extract was recommended to the patient by the medical staff as a preventive agent.

Case 6

A female, age 40, was diagnosed with breast cancer. The patient underwent chemotherapy and after the chemotherapy was prescribed to take the curcumin and turmeric extract solution of Example 1 (2ml in a glass of water 2 times a day, on an empty stomach). The patient was prescribed by her physician to continue taking curcumin and turmeric extract as a preventive measure for an indefinite period.

Case 7

A male aged 50 who suffers from multiple myeloma received the curcumin and turmeric extract solution of Example 1 (2ml in a glass of water 3 times a day, on an empty stomach). The patient was given the curcumin and turmeric extract for a year. For the first 10 months there was a significant improvement. Afterwards, the multiple myeloma patient exhibited fatigue and was prescribed Velcade treatment in addition to curcumin and
turmeric extract. He was prescribed to continue taking the curcumin and turmeric extract and reported improvement in his condition.

Case 8
A nine year old female child with neuroblastoma received a bone marrow implantation. The curcumin and turmeric extract solution of example 2 (2ml in a glass of water 3 times a day, on an empty stomach) was administered to her for the last 24 months.

The child has exhibited improvement since she started taking liquid curcumin and turmeric extract, 2 ml (example 2) 3 times daily on an empty stomach. Recently, she underwent bone marrow implantation. She keeps improving with the curcumin and turmeric extract (Example 2)

Case 9
A 45 year old female with high cholesterol (170 mg/dl of Cholesterol LDL). Tried unsuccessfully a variety of statins for lowering her cholesterol .

After failing to get any improvement in her cholesterol levels, the patient received the curcumin and turmeric extract of example 3, 5ml in a glass of water X twice a day on an empty stomach. Significant improvement in cholesterol levels was noted after 2 weeks of treatment. The patient keeps taking the curcumin and turmeric extract and reports on lower cholesterol levels.

Case 10
A 70 year old male with Alzheimer's disease. Received the curcumin and turmeric extract of example 3, 5ml in a glass of water X three times a day on an empty stomach. Significant improvement in his cognitive abilities was noted after 4 weeks of treatment. The patient keeps taking the curcumin and turmeric extract and reports on improvement in his condition.

Case 11
A 50 year old male with Crohn's disease. Received the curcumin and turmeric extract of example 3, 5ml in a glass of water X twice a day on an empty stomach. During the three months of taking the curcumin and turmeric extract the patient did not take any other medicine or supplement. He reported significant improvement in the symptoms of the Crohn's
disease. The patient keeps taking the curcumin and turmeric extract and keeps reporting on improvement in his condition.

Case 12

A 12 year old female child with constant constipation was prescribed to take curcumin and turmeric extract of example 3, 5ml in a glass of water, twice a day.

The girl reported on significant improvement in her condition after taking the extract for two weeks.

Case 13

A 60 year old male with Parkinson's disease. Received the curcumin and turmeric extract of example 3, 5ml in a glass of water X three times a day on an empty stomach. Significant improvement in his condition was noted after 3 weeks of treatment. The patient keeps taking the curcumin and turmeric extract and reports on improvement in his condition.

Curcumin provided orally or intraperitoneally to rats, is mostly egested in the feces and only a little in the urine. Only traces of curcumin were found in the blood. Also, the bio-availability of curcumin given orally in most of the commercially available capsules is very low.

The curcumin and turmeric extracts of the present invention demonstrate a much better absorption rate than do most of the commercially available curcumin capsules.

The extracts of the present invention show high bio-availability and have been found to be pharmacologically safe.

Over the 45 months period of clinical trials, the curcumin and turmeric extracts appear to have high bioavailability and appear to be devoid of any unpleasant side effects. The curcumin and turmeric extract products of the present invention have been shown to have high bio-availability in contrast to most of the curcumin capsules that are commercially available, even when compared to curcumin capsules that contain Terikatu.

It would appear that the products of the present invention are well absorbed by the blood and thus can reach all organs in a patient. The higher bioavailability of the curcumin and turmeric extracts of the present
invention therefore enhance healing and recovery in a variety of clinical conditions.

The efficacy, pharmacological safety and cost effectiveness of the liquid curcumin and turmeric extracts of the present invention have been demonstrated here.

The liquid curcumin and turmeric extracts of the present invention are suitable for oral administration, and appear to be well absorbed through the intestine to the blood and thus exhibit the potential to heal a wide range of cancerous organs and inflammatory conditions, such as, but not limited to those mentioned by Chattopadhyay et al. Current Science 87(1) July 2004, 44-53.

The extract described here is extracted from the curcuminoids that are the active ingredients of turmeric as well as the powder of the whole root of the turmeric. The application of the present invention may also include all the parts of the turmeric plant, which exhibit medicinal activity, as is described by Betancor-Fernandez A. et al., see also: "Curcumin derived from Turmeric (Curcuma longa): a spice for all seasons", by B. B. Aggarwal et al. pp 350-387, in the book: "Phytopharmaceuticals in Cancer Prevention", CRC 2005.

The references cited herein teach many principles that are applicable to the present invention. Therefore the full contents of these publications are incorporated by reference herein where appropriate for teachings of additional or alternative details, features and/or technical background.

It is to be understood that the invention is not limited in its application to the details set forth in the description contained herein or illustrated in the drawings. The invention is capable of other embodiments and of being practiced and carried out in various ways. Those skilled in the art will readily appreciate that various modifications and changes that can be applied to the embodiments of the invention as hereinbefore described without departing from its scope, defined in and by the appended claims.
WHAT IS CLAIMED IS:

1. The use of a composition comprising ethanol, curcumin and a dissolved whole turmeric powder for the preparation of an alcoholic curcumin and turmeric liquid pharmaceutical composition for treating proliferative and other clinical disorders in a human patient said composition evidencing enhanced bioavailability vis-à-vis a comparable dosage of curcumin in dry powder form.

2. The use according to claim 1 wherein said composition further comprises at least one alcohol-extracted component of propolis.

3. The use according to claim 1 wherein said composition further comprises at least one alcohol-extracted component of ginger.

4. The use according to claim 1 wherein said composition further comprises at least one alcohol-extracted component of Lippia citriodora

5. The use according to claim 1 wherein said composition further comprises glycerin.

6. The use according to claim 1 wherein the proliferative disorder is selected from the group consisting of a myeloma, multiple myeloma, breast cancer, neuroblastoma, colorectal cancer, prostate cancer, pancreatic cancer, a malignant tumor, brain stem glioma, as well as other clinical disorders such as Alzheimer's disease, Crohn's disease, high cholesterol levels, Parkinson's disease, constipation and more.

7. The use according to claim 1 wherein the composition is adapted to be absorbed from the intestine into the bloodstream of the human patient with a high bioavailability.

8. The use according to claim 1 wherein said composition is prepared using an alcoholic extract of whole turmeric powder.

9. The use according to claim 1 wherein said composition is prepared using an alcoholic extract of curcumin.

10. The use according to claim 1 wherein said curcumin comprises a plurality of curcuminoïdes.

11. The use of a composition comprising a mixture of an alcohol and oil, curcumin and a dissolved whole turmeric powder for the preparation of a curcumin and turmeric liquid pharmaceutical composition for treating
proliferative and other clinical disorders in a human patient said composition
evidencing enhanced bioavailability vis-à-vis a comparable dosage of
curcumin in dry powder form.

12. The use of a composition according to claim 11 wherein said
composition is adapted to be absorbed into the lymphatic system.

13. The use of a composition according to claim 1 wherein said
composition further comprises a pharmaceutically acceptable carrier.

14. A method for preparing a medicament for treating a proliferative
and other disorders in a human patient, the method comprising:

(a) extracting at least one plant powder comprising whole
turmeric in heated ethanol; and

(b) extracting curcumin in heated ethanol; and

(c) combining said extracts to form an ethanolic curcumin
and turmeric composition.

15. A method according to claim 14 further comprising extracting at
least one further plant powder selected from the group consisting of
propolis powder, ginger and Aloysia (Lippia citriodora)

16. A method according to claim 14, wherein the ethanolic curcumin
and turmeric composition comprises curcuminoids: selected from the group
consisting of curcumin (diferuloylmethane), demethoxycurcumin and bis-
demethoxycurcumin, as well as volatile compounds of turmeric.

17. A method according to any of claim 14, wherein the extracting steps
comprise heating the ethanol to about its boiling point.

18. A method according to claim 14, wherein the extracting steps
further comprise cooling the ethanolic turmeric and curcumin extracts to
about 60°C.

19. A method according to claim 18, wherein the extracting steps
further comprise heating the ethanolic curcumin and turmeric extracts to
about its boiling point after the cooling step.

20. A method according to claim 14, further comprising:

(d) filtering the ethanolic curcumin and turmeric extract to remove
undissolved solids.
21. A method according to any of claim 14, further comprising mixing glycerin with ethanol and curcumin and turmeric powder.

22. A method according to claim 21, wherein the glycerin is preheated to around 80°C.

23. Use according to claim 1, wherein the proliferative disorder is selected from a myeloma, multiple myeloma, breast cancer, neuroblastoma, colorectal cancer, prostate cancer, pancreatic cancer, a malignant tumor, brain stem glioma and other clinical disorders.

24. A method for treating a proliferative or clinical disorder in a human patient comprising administering to said patient a pharmaceutically effective amount of the alcoholic curcumin and turmeric liquid composition comprising ethanol, curcumin and a dissolved whole turmeric powder.

A method according to claim 24, wherein the proliferative disorder is selected from a myeloma, multiple myeloma, breast cancer, neuroblastoma, colorectal cancer, prostate cancer, pancreatic cancer, a malignant tumor, and brain stem glioma.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K36/9066 A61K36/9068

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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 practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>X</td>
<td>KIRANA C ET AL: &quot;Screening for antitumor activity of 11 species of Indonesian zingiberaceae using human MCF-7 and HT-29 cancer cells&quot; PHARMACEUTICAL BIOLOGY, SWETS AND ZEITLINGER, LISSE, NL, vol. 27, no. 1, 1 June 2005 (2005-06-01), pages 271-276, XP009100220 ISSN: 1388-0209 page 273; table 1</td>
<td>1-25</td>
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Further documents are listed in the continuation of Box C.

X See patent family annex.

* 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 document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or 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.

"S" document member of the same patent family

Date of the actual completion of the international search

21 May 2008

Date of mailing of the international search report

05/06/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

Thalmair-De Meyere
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<td>KUTTAN R ET AL: &quot;TURMERIC AND CURCUMIN AS TOPICAL AGENTS IN CANCER THERAPY&quot; TUMORI, XX, IT, vol. 73, no. 1, 1 January 1987 (1987-01-01), pages 29-32, XP009083110 ISSN: 0300-8916 the whole document</td>
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<td>REDKAR R G ET AL: &quot;Natural products as anticancer agents&quot;&lt;br&gt;INDIAN DRUGS 200311 IN,&lt;br&gt;vol. 40, no. 11, November 2003 (2003-11),&lt;br&gt;pages 619-626, XP009100416&lt;br&gt;ISSN: 0019-462X&lt;br&gt;the whole document _____</td>
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INTERNATIONAL SEARCH REPORT

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

   Although claims 24,25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. □ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. □ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This international Searching Authority found multiple inventions in this international application, as follows:

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

□ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

□ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

□ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
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<td>27-04-2005</td>
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