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(54) Title: METHOD FOR THE MANAGEMENT OF CANCER AND TREATMENT OF CANCER COMORBIDITIES

(57) Abstract: A method for the management of cancer and treatment of cancer comorbidities, including but not limited to cancer-related fatigue, cachexia, anorexia, pain, anemia, asthenia, depression, muscle weakness, nausea, vomiting, skin, and skin appendages adverse reactions; said method comprising the administration by the conventional and non-conventional oral, topical, parenteral routes and intra-tumoral injection, or in combination thereof, or the administration as adjuvant potentiator in other therapies using the forenamed routes, of a composition containing as active ingredient an extract of *Allium species*, which contains querceting, an extract of *Citrus species* and an extract of *Paullinia species* and an extract of *Theobroma species*.



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METHOD FOR THE MANAGEMENT OF CANCER
AND CANCER TREATMENT-RELATED COMORBIDITIES

5 TECHNICAL FIELD

 The invention concerns a method for the management of cancer and treatment cancer comorbidities, including but not limited to cancer-related fatigue, cachexia, anorexia, pain, anemia, asthenia, depression, impaired cognitive function, loss of appetite, muscle weakness, nausea, vomiting, arthritis, organ
10 damage, including but not limited to radiation-induced burns, heart disorders due to cardiotoxicity by chemo- and radiotherapy, hypertension, thromboembolism, occasional chest pain, difficulty in breathing, shortness of breath, dizziness, fainting, pallor (pale skin or lips), headaches, difficulty in concentrating, insomnia, difficulty in staying warm, bleeding problems, nail damages, and skin appendages
15 adverse reactions, exemplified by irritation and dry skin, sore and dry ulcerated mouths.

BACKGROUND OF THE INVENTION

 So far, the main anti-cancer therapeutic strategies have consisted in
20 inhibiting the non-controlled cell proliferation. Nonetheless, as tumour evolution has multifaceted mechanisms, more strategies should be considered in order to address the remaining gaps in cancer management, and more importantly in alleviating the side effects of cancer treatments. Previous research indicates that inflammatory cells and pro-inflammatory molecules mostly contribute to tumor
25 growth and progression. In experimental settings, reduction of inflammatory molecules (e.g. cytokines) inhibits cancer development. Based on earlier research, blockade of inflammation appears to be a relevant strategy for management of

cancer. Therefore, controlling or reducing such a process of “malignant flame” (inflammation) represents a crucial approach in the management of cancer.

Anticancer therapies have extended patients’ life expectancy; however, cancer-related and its treatment-related comorbidities have become an issue for cancer survivors. The above mentioned disorders are among the most feared side-effects of anticancer agents so that the quality of life (QoL), as well as the life expectancy might be countered by reduced QoL and increased mortality.

Asthenia fatigue syndrome (AFS) or cancer-related fatigue is a common symptom perceived during and after treatment by patients with cancer and consists of pathologic fatigue, poor endurance, and impaired motor and cognitive function. It is a symptom, difficult to define, with a set of vague sensations, different for each patient. Some studies in cancer have reported the findings about how the above-mentioned comorbidities can increase the severity of cancer related fatigue.

A growing body of research has examined the hypothesis that cancer-related fatigue is driven by activation of the pro-inflammatory cytokine network. Actually, inflammation appears to play an essential role in cancer-related fatigue before, during and after cancer therapies. Accordingly, controlling or reducing the persistent inflammatory process can be beneficial to the management of cancer related fatigue.

The persistent pathological conditions in cancer patients may favour up-regulated expressions of pro-inflammatory mediators / cytokines and cause a sustained high level of chronic inflammation in the whole body, forming an important ground for triggering the comorbidities of cancer.

In the context of cancer treatment, anti-cancer chemo-agents destroy rapidly dividing cancer cells, as well as all the fast dividing non-cancer cells, which

undergo apoptosis due to chemotherapy agents and radiotherapy attack. The massive apoptosis of so many non-cancerous cells results in a large amount of secondary necrotic cells. These necrotic cells will cause and sustain inflammation by stimulating production of pro-inflammatory molecules.

5 Many internal and external factors can contribute to unwanted prolonged inflammation. However, activated vascular endothelial cells (ECs) in the human vasculature, as they are in direct contact with blood, play pivotal roles in the development of acute and chronic inflammation. Therefore, vascular EC may represent a relevant therapeutic target for the management of cancer and
10 treatment of cancer comorbidities, including but not limited to cancer-related fatigue, cachexia, anorexia, pain, anemia, asthenia, depression, muscle weakness, nausea, vomiting, skin and skin appendages adverse reactions.

One of the possible mechanisms by which inflammation may contribute to the development of tumorigenesis includes enhanced expression of pro-
15 inflammatory mediators such as cytokines (e.g. Interleukin 8) and adhesion molecules, e.g. ICAM-1 (Intercellular Adhesion Molecule 1, also known as CD54), E-selectin/ELAM-1 (also known as CD62E). The adhesion molecules can be found in low concentrations in the membranes of endothelial cells that "line" the interior surface of blood vessels in the whole vascular system. Their expression
20 levels are essential in the inflammatory process. A lower expression of such pro-inflammatory molecules indicates lesser inflammation, while higher expression indicates augmented inflammatory status. Upon toxic or pathological insults, the produced TNF-alpha (Tumor Necrosis Factor) will greatly stimulate expression of adhesion molecules and cytokines exemplified by E-selectin, ICAM-1 and
25 Interleukin 8 (IL-8). Increased expressions of adhesion molecules and cytokines mediate immune and inflammatory responses via recruitment of leukocytes to

inflammatory sites (infiltration of inflammatory cells through local vascular endothelium).

A former study showed that, compared with controls, the levels of soluble E-selectin and ICAM-1 were significantly higher in breast cancer patients at late stage. Besides, elevated adhesion molecule levels were predictive of decreased survival.

In addition, various pro-inflammatory mediators may not only switch on the tumor-prone inflammatory angiogenesis, a process that is essentially controlled by vascular endothelial growth factor, but also promote tumor metastasis.

Hence, for reducing harmful inflammation, it is critical to limit the synthesis of these pro-inflammatory molecules so as to decrease the anomalous inflammatory response.

Our studies show that, at molecular level, a composition comprising the ingredients mentioned hereafter is an anti-inflammatory agent, capable of reducing TNF α induced expression of adhesion molecules ICAM-1 and E-selectin on HUVECs (Human Umbilical Vein Endothelial Cells), as well as the cytokine IL-8 expression. Such anti-inflammatory potential results in inhibition of tumour progression and reduction of tumor size (see in the section above and data in the examples, obtained from both *in vitro* and *in vivo* studies). Thus, a composition comprising the ingredients mentioned hereafter provides anti-inflammatory effect for the support management of cancer and treatment of cancer comorbidities.

A composition comprising the ingredients mentioned hereafter was subcutaneously injected into a mouse cancer model in a randomized experiment. It was observed that, compared to non-treated mice, the said composition inhibits tumor growth and tumor size in treated mice (see data in the example 2 obtained from both *in vitro* and *in vivo* studies).

A composition comprising the ingredients mentioned hereafter was used in a topical formulation by cancer patients in order to prevent chemotherapy induced alopecia. Some patients reported that, apart from the beneficial effect on unwanted hair loss, other symptoms, such as fatigue, which they were also suffering from, started to improve steadily.

SUMMARY OF THE INVENTION

A composition comprising the ingredients mentioned hereafter was used orally by a patient suffering from liver cancer. Based on the physicians and patient's report and pictures taken before and after the intake of the said composition, his general state turned out to improve significantly, including alleviation of cancer related fatigue.

It has been discovered that the administration by oral route, topical, or parenteral route, intra-tumoral injection, or a combination thereof, of a composition containing as active ingredient an extract of *Allium species*, which may contain quercetin, an extract of *Citrus species* and an extract of *Paullinia species* and an extract of *Theobroma species*, has a novel and previously unknown effect for the management of cancer and treatment of cancer comorbidities.

The present invention proposes a method for the management of cancer and treatment of cancer comorbidities, including but not limited to cancer-related fatigue, cachexia, anorexia, pain, anemia, asthenia, depression, muscle weakness, nausea, vomiting, skin and skin appendages adverse reactions; comprising the administration by both conventional and non-conventional routes, and or as adjuvant potentiator in cell therapies, or topical route, or parenteral route, or intra-tumoral injection, or in combination, of a composition containing as

active ingredient an extract of *Allium species*, which preferably contain quercetin, an extract of *Citrus species* and an extract of *Paullinia species* and an extract of *Theobroma species*.

5 BRIEF DESCRIPTION OF THE FIGURES

Figure 1 corresponds to the curves of the mean body weight (in grams) measured at different times.

Figure 2 corresponds to the curves of the mean tumor volume (in mm³)
10 measured at different times.

DETAILED DESCRIPTION OF THE INVENTION

In particular, the present invention concerns a method for the
15 management of cancer and treatment of cancer comorbidities, including but not limited to cancer-related fatigue, cachexia, anorexia, pain, anemia, asthenia, depression, impaired cognitive function, loss of appetite, muscle weakness, nausea, vomiting, arthritis, organ damage, including but not limited to radiation-induced burns, heart disorders due to cardiotoxicity by chemo- and radiotherapy,
20 hypertension, thromboembolism, occasional chest pain, difficulty in breathing, shortness of breath, dizziness, fainting, pallor (pale skin or lips), headaches, difficulty in concentrating, insomnia, difficulty in staying warm, bleeding problems, nail damages, and skin appendages adverse reactions, exemplified by irritation and dry skin, sore and dry ulcerated mouths; comprising the administration by oral
25 route, topical, or parenteral route, intra-tumoral injection, or a combination thereof, of a composition containing as active ingredient an extract of *Allium*

species, which may contain quercetin, an extract of *Citrus species* and an extract of *Paullinia species* and an extract of *Theobroma species*.

Among the methods for the management of t cancer and treatment of cancer comorbidities, according to the invention, those which are of more particular interest are the methods in which the preferred oral composition contains from 30% to 93% by weight of an extract of *Allium species*, which contains quercetin, from 3% to 33% by weight of an extract of *Citrus species*, from 0.10% to 2.5% by weight of an extract (atomized or not) of *Paullinia species* and from 0.10% to 2.5% by weight of an extract (atomized or not) of *Theobroma species*, based on the total weight of the four active ingredients.

According to an embodiment, the composition comprises from 30% to 93% by weight of an extract of *Allium species*, which contains quercetin, from 3% to 33% by weight of an extract of *Citrus species*, from 0.10% to 2.5% by weight of an extract (atomized or not) of *Paullinia species*, from 0.10% to 2.5% by weight of an extract (atomized or not) of *Theobroma species*, from 0.5% to 3.0% by weight of Sodium chloride and from 25% to 50% by weight of Glycerin, based on the total weight of the composition.

Among the methods for the management of cancer and treatment of cancer comorbidities, those which are the more preferred interest are the methods in which the compositions are used not only as conventional oral composition, composition for injection, topical application, but also as an adjuvant potentiator in for the management of cancer and its treatment-related comorbidities. The compositions contain from 30% to 93% by weight of an extract of *Allium species*,

which contains quercetin, from 3% to 33% by weight of an extract of *Citrus species*, from 0.10% to 2.5% by weight of an extract (atomized or not) of *Paullinia species* and from 0.10% to 2.5% by weight of an extract (atomized or not) of *Theobroma species*, based on the weight of the four active ingredients.

5

According to an embodiment, the compositions contain from 30% to 93% by weight of an extract of *Allium cepa*, from 3% to 33% by weight of an extract of *Citrus lemon*, from 0.10% to 2.5% by weight of an extract (atomized or not) of *Paullinia species* and from 0.10% to 2.5% by weight of an extract (atomized or not) of *Theobroma species*, based on the weight of the four active ingredients.

10

According to an embodiment, the composition contains from 30% to 93% by weight of an extract of *Allium species*, which contains quercetin, from 3% to 33% by weight of an extract of *Citrus species*, from 0.10% to 2.5% by weight of an extract (atomized or not) of *Paullinia species*, from 0.10% to 2.5% by weight of an extract (atomized or not) of *Theobroma species*, from 0.5% to 3.0% by weight of Sodium chloride and from 25% to 50% by weight of Glycerin, based on the total weight of the composition.

15

The term extract of *Allium species* refers particularly to extracts and native extracts obtained from all species of the genus *Allium* (family *Liliaceae*) and especially *Allium cepa*, which may contain quercetin. The term extract of *Citrus species* refers particularly to extracts and native extracts obtained from all species of the genus *Citrus* (family *Rutaceae*) and especially *Citrus lemon*. The term extract (atomised or not) of *Paullinia species* refers particularly to extracts and native extracts obtained from all species of the genus *Paullinia* (family

20

25

Sapindaceae) and especially *Paullinia cupana*. The term extract (atomised or not) of *Theobroma species* refers particularly to aqueous-alcoholic extracts and native extracts obtained from all species of the genus *Theobroma* (family *Malvaceae*) and especially *Theobroma cacao*.

5

The most preferred compositions used according to the invention are: those containing approximately 87% by weight of an extract of *Allium cepa*, which contains quercetin, approximately 12% by weight of an extract of *Citrus lemon*, approximately 0.5% by weight of an extract (atomized or not) of *Paullinia cupana* and approximately 0.5% by weight of an extract (atomized or not) of *Theobroma cacao*, based on the total weight of the four active ingredients.

10

According to the invention, the composition is chronically administered in a mixture containing as active ingredient an extract of *Allium species*, which contains quercetin, an extract of *Citrus species* and an extract of *Paullinia species* and an extract of *Theobroma species*.

15

According to an embodiment of the invention the composition is administered daily during a period of several months or longer with a composition containing as active ingredient an extract of *Allium species*, which contains quercetin, an extract of *Citrus species* and an extract of *Paullinia species* and an extract of *Theobroma species*.

20

In order to obtain a measurable effect on the management of cancer and treatment of cancer comorbidities, it is necessary to perform the administration of the compositions chronically, preferably during at least 6 months.

25

When using the compositions obtained according to the invention, doses may vary within relatively wide limits and must be set according to the person being treated and the condition concerned. Pharmaceutical compositions normally contain from 0.4 to 1000 mg, preferably from 2 to 400 mg, of active ingredients as defined
5 above, in the form of dry extract.

The present invention also concerns a composition containing as active ingredient an extract of *Allium* species, which contains quercetin, an extract of Citrus species and an extract of *Paullinia* species and an extract of *Theobroma*
10 species for use in the management of cancer and for the treatment of cancer comorbidities, including but not limited to cancer-related fatigue, cachexia, anorexia, pain, anemia, asthenia, depression, muscle weakness, nausea, vomiting, skin, and skin appendages adverse reactions; by both conventional and non-conventional routes, and/or as adjuvant potentiator in cell therapies, or topical
15 route, or parenteral route, or intra-tumoral injection, or in combination thereof.

According to an embodiment of the invention the composition for use in the management of cancer and for the treatment of cancer comorbidities contains an extract of *Allium* species, which contains quercetin, an extract of Citrus species
20 and an extract (atomized or not) of *Paullinia* species and an extract (atomized or not) of *Theobroma* species.

According to a further embodiment of the invention the composition for use in the management of cancer and for the treatment of cancer comorbidities,
25 contains from 30% to 93% by weight of an extract of *Allium* species, which contains quercetin, from 3% to 33% by weight of an extract of Citrus species, from

0.10% to 2.5% by weight of an extract (atomized or not) of Paullinia species and from 0.10% to 2.5% by weight of an extract (atomized or not) of Theobroma species, based on the total weight of the four active ingredients.

EXAMPLE OF TREATMENT

The patients have received, every day by oral, topical, parenteral routes, or intratumoral injection, alone or in combination, a treatment containing :

- an extract of *Allium cepa* (containing querceting): 87.04 %
- 5 - an extract of *Citrus lemon*: 11.96 %
- an atomised extract of *Paullinia cupana*: 0.50 %
- an atomised extract of *Theobroma cacao*: 0.50 %

(hereafter composition A).

This lotion has been prepared as indicated in example 1 of patent application WO
10 2008/113912.

Composition A which is a mixture of four natural ingredients has been reported to beneficially affect defects in abnormal cell apoptosis, as well as in inflammatory processes. This has indicated that composition A is capable of affecting positively in the management of the above-mentioned cancer and cancer
15 treatment related comorbidities.

Example 1: Study of the composition, containing as active ingredient an extract of *Allium* species, which contains quercetin, an extract of *Citrus* species and an extract of *Paullinia* species and an extract of *Theobroma* species, on its anti-inflammatory effect via inhibiting TNF alpha-induced expression of pro-inflammatory molecules: ICAM-1, E-selectin and Interleukin 8, as summarized
20 Table 2a, 2b and 2c).

Table 1. The tested compositions

Compound	Ingredient	in total %wt
A	Allium Cepa	50,0
	Citrus	50,0
B	Allium Cepa	87,5
	Citrus	12,5
C	Allium Cepa	87,0
	Citrus	12,0
	Guarana dry extract	0,5
	Cacao dry extract	0,5
Control	Medium	

Table 2a. The effects of “compositions” on the expression of adhesion molecule **ICAM-1 (CD54)** on the surface of endothelial cells (HUVECs)

Composition	Non-treated cells measured by sABC*	TNF-treated cells measured by sABC*	% Increase (+) % Reduction (-) compared to control
Medium (control)	3 172	386 181	
A	2 061	296 561	-23%
B	1 947	297 444	-23%
C	1 664	254 171	-34%

* specific Antibody Bound per Cell

Table 2b. The effects of “compositions” on the expression of adhesion molecule **E-selectin/ELAM-1 (CD62E)** on the surface of endothelial cells (HUVECs)

Composition	Non-treated cells measured by sABC*	TNF-treated cells measured by sABC*	% Increase (+) % Reduction (-) compared to control
Medium (control)	Non detectable	3 074	
A	251	4 235	+38%
B	186	3 447	+12%
C	65	1 648	-46%

* specific Antibody Bound per Cell

Table 2c. The effects of “**compositions**” on the expression of cytokine **Interleukin 8 (IL-8)** by endothelial cells (HUVECs)

Composition	Non-treated cells measured by sABC*	TNF-treated cells measured by sABC*	% Increase (+) % Reduction (-) compared to control
Medium (control)	1 164	5 406	
A	1 067	6 274	+16%
B	1 015	5 563	+3%
C	887	4 827	-11%

* specific Antibody Bound per Cell

Example 2: Study on the anti-tumor activity of a new “composition” using nude mice carrying subcutaneous human tumor of type KB.

Figure 1 illustrates the curves of the average weight of nude mice bearing subcutaneous human tumor type KB. Mice were randomized at Day 7 and received a daily injection of 100 µl composition solution (THI) of 0.3% and 1.0% respectively for five consecutive days.

In Figure 1, *x-axis* represents time (days); *y-axis* represents average weight of nude mice (g). Blue (curve 2): control vehicle; Pink (curve 3): composition (THI) of 0.3%; Yellow (curve 1): composition (THI) of 1%. No significant weight changes were observed.

Figure 2 illustrates the curves of the mean tumor volume of nude mice bearing subcutaneous human tumor type KB. Mice were randomized at Day 7 and received a daily injection of 100 µl composition solution (THI) of 0.3% and 1.0% respectively for five consecutive days.

In Figure 2, *x-axis* represents time (days); *y-axis* represents average tumor volume of nude mice (mm³). Blue (curve 2): control vehicle; Pink (curve 3): composition (THI) of 0.3%; Yellow (curve 1): composition (THI) of 1%. No

significant weight changes were observed. Composition (THI) 0.3% show anti-tumor effect compared to control.

CLAIMS

1. A method for the management of cancer and for the treatment of cancer comorbidities, including but not limited to cancer-related fatigue, cachexia, anorexia, pain, anemia, asthenia, depression, muscle weakness, nausea, vomiting, skin, and skin appendages adverse reactions; said method comprising the administration by both conventional and non-conventional routes, and/or as adjuvant potentiator in cell therapies, or topical route, or parenteral route, or intra-tumoral injection, or in combination thereof, of a composition containing as active ingredient an extract of *Allium species*, which contains quercetin, an extract of *Citrus species* and an extract of *Paullinia species* and an extract of *Theobroma species*.
2. A method for the management of cancer and for the treatment of cancer comorbidities according to claim 1, wherein the composition contains an extract of *Allium species*, which contains quercetin, an extract of *Citrus species* and an extract (atomized or not) of *Paullinia species* and an extract (atomized or not) of *Theobroma species*.
3. A method for the management of cancer and for the treatment of cancer comorbidities, according to claims 1 and 2, wherein the composition contains from 30% to 93% by weight of an extract of *Allium species*, which contains quercetin, from 3% to 33% by weight of an extract of *Citrus species*, from 0.10% to 2.5% by weight of an

extract (atomized or not) of Paullinia species and from 0.10% to 2.5% by weight of an extract (atomized or not) of Theobroma species, based on the total weight of the four active ingredients.

Figure 1

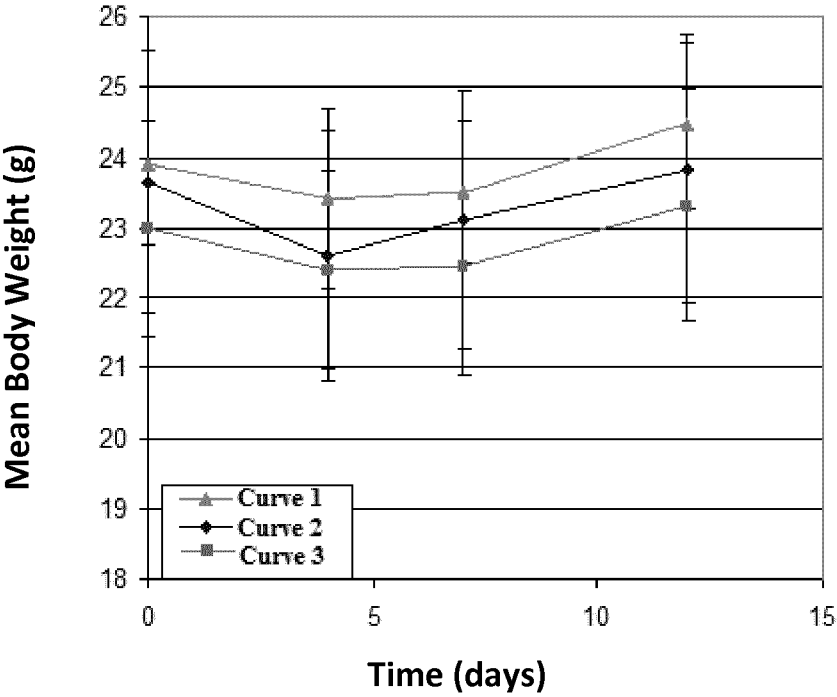
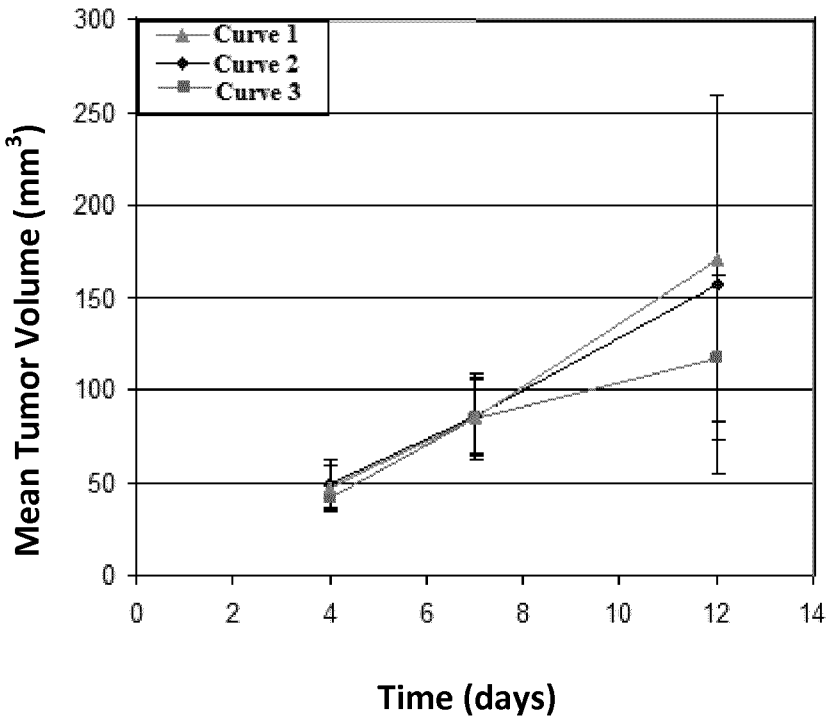


Figure 2



INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER		
INV.	A61K36/752 A61P35/00	A61K36/77 A61K36/8962 A61K36/00 A61K36/185
ADD.		
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 practicable, search terms used) EPO-Internal, BIOSIS, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2012/113820 A1 (LEGACY HEALTHCARE HOLDING LTD [MT]; HARTI SAAD [CH]) 30 August 2012 (2012-08-30) page 4, paragraph 2 - page 5, paragraph 2 page 13, paragraph 3 -----	1-3
Y	WO 2013/020719 A2 (LEGACY HEALTHCARE HOLDING LTD [MT]; HARTI SAAD [CH]) 14 February 2013 (2013-02-14) page 8, paragraph 2 - page 10, paragraph 2; claims 1-8 ----- -/--	1-3
☒ Further documents are listed in the continuation of Box C. ☒ 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 application or patent 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 "&" document member of the same patent family		
Date of the actual completion of the international search 9 January 2015		Date of mailing of the international search report 21/01/2015
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Zellner, Eveline

INTERNATIONAL SEARCH REPORT

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Information on patent family members

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(54) 发明名称

用于管理癌症和治疗癌症并存病的方法

(57) 摘要

一种用于管理癌症和用于治疗癌症并存病的方法,所述癌症并存病包括但不限于癌症相关的疲劳、恶病质、厌食、疼痛、贫血、虚弱、抑郁、肌无力、恶心、呕吐、皮肤和皮肤附属结构不良反应;所述方法包括施用含有葱属物种提取物、柑橘属物种提取物、泡林藤属物种提取物和可可属物种提取物作为活性成分的组合,所述葱属物种提取物含有槲皮素,所述组合物通过常规或非口服、局部、胃肠外途径和肿瘤内注射,或其组合施用,或通过前述途径施用所述组合物作为其它疗法中的辅助增效剂。

1. 一种用于管理癌症和用于治疗癌症并存病的方法,所述癌症并存病包括但不限于癌症相关的疲劳、恶病质、厌食、疼痛、贫血、虚弱、抑郁、肌无力、恶心、呕吐、皮肤和皮肤附属结构不良反应;所述方法包括施用含有葱属物种提取物、柑橘属物种提取物、泡林藤属物种提取物和可可属物种提取物作为活性成分的组合,所述葱属物种提取物含有槲皮素,所述组合物通过常规和非常规途径,和/或作为细胞疗法中的辅助增效剂,或局部途径,或胃肠外途径,或肿瘤内注射,或其组合而施用。

2. 权利要求1的用于管理癌症和用于治疗癌症并存病的方法,其中所述组合物含有葱属物种提取物、柑橘属物种提取物、泡林藤属物种提取物(粉化或未粉化)和可可属物种提取物(粉化或未粉化),所述葱属物种提取物含有槲皮素。

3. 权利要求1或2的用于管理癌症和用于治疗癌症并存病的方法,其中基于四种活性成分的总重量,所述组合物含有30%至93%重量百分比的葱属物种提取物、3%至33%重量百分比的柑橘属物种提取物、0.10%至2.5%重量百分比的泡林藤属物种提取物(粉化或未粉化)和0.10%至2.5%重量百分比的可可属物种提取物(粉化或未粉化),其中所述葱属物种提取物含有槲皮素。

用于管理癌症和治疗癌症并存病的方法

技术领域

[0001] 本发明关注用于管理癌症和治疗癌症并存病的方法,所述癌症并存病包括但不限于癌症相关的疲劳、恶病质、厌食、疼痛、贫血、虚弱、抑郁、认知功能受损、食欲不振、肌无力、恶心、呕吐、关节炎、器官损伤(包括但不限于放射诱导的烧伤、化疗和放疗的心脏毒性导致的心脏病)、高血压、血栓栓塞、偶发性胸痛、呼吸困难、呼吸短促、头晕、昏厥、苍白(苍白的皮肤和嘴唇)、头痛、难以集中注意力、失眠、难以保暖、流血问题、指甲损伤和皮肤附属结构不良反应,例如皮肤刺激和干燥、痛性和干燥性口腔溃疡。

背景技术

[0002] 迄今为止,主要的抗癌治疗策略包括抑制不受控制的细胞增殖。但是,因为肿瘤演变具有多层面的机制,应该考虑更多策略以处理癌症管理中还存在的缺口,并且更重要的是,缓解癌症治疗的副作用。先前的研究表明,炎性细胞和促炎性分子主要有助于肿瘤生长和进展。在实验设置中,炎性分子(例如细胞因子)的减少已知肿瘤发展。基于较早的研究,阻塞炎症似乎是癌症管理的相关策略。因此,控制或减少这样的“恶性火焰”(炎症)的过程代表癌症管理中的重要方法。

[0003] 抗癌疗法延长患者生命预期;然而,癌症相关的和其治疗相关的并存病成为癌症幸存者的问题。上面提及的疾病属于最担心的抗癌剂的副作用,对生活质量(QoL),以及生命预期不利,会降低QoL并提高死亡率。

[0004] 虚弱疲劳综合征(AFS)或癌症相关的疲劳是癌症患者在治疗期间和治疗之后感受到的常见症状,并且由病理性疲劳、缺乏耐力以及运动和认知功能受损组成。其是难以定义的症状,具有一组模糊的感觉,各患者不同。一些癌症研究报道了关于上面提及的并存病如何能够提高癌症相关的疲劳的严重性的发现。

[0005] 越来越多的研究检验了癌症相关的疲劳由促炎性细胞因子网络的激活驱动的假说。事实上,炎症似乎在癌症疗法之前、期间和之后的癌症相关的疲劳中起至关重要的作用。因此,控制或减少顽固性炎症过程可以有利于管理癌症相关的疲劳。

[0006] 癌症患者中的顽固性病理学病症可能偏爱促炎性介质/细胞因子表达上调,并导致全身持久的高水平慢性炎症,形成启动癌症并存病的重要基础。

[0007] 在癌症治疗的背景下,抗癌化学剂破坏快速分裂的癌细胞,以及所有快速分裂的非癌细胞,其经历由化疗剂和放疗攻击造成的细胞凋亡。如此多非癌细胞的大量凋亡导致了大量次生坏死细胞。这些坏死细胞会通过产生促炎性分子导致并维持炎症。

[0008] 许多内部和外部因素能够有助于不想要的延长的炎症。然而,人脉管系统中的活化的血管内皮细胞(EC)由于直接接触血液而在急性和慢性炎症的发展中其关键作用。因此,血管EC可能代表管理癌症和治疗癌症并存病的相关治疗靶标,所述癌症并存病包括但不限于癌症相关的疲劳、恶病质、厌食、疼痛、贫血、虚弱、抑郁、肌无力、恶心、呕吐、皮肤和皮肤附属结构不良反应。

[0009] 炎症有助于肿瘤发生的发展的可能机制之一包括促炎性介质如细胞因子(例如白

介素8)和粘附分子例如ICAM-1(细胞内粘附分子1,也称为CD54)、E-选择素/ELAM-1(也称为CD62E)表达增强。可以在内皮细胞的膜上发现低密度的粘附分子,所述内皮细胞在整个脉管系统中沿血管的内表面排列。其表达水平在炎症过程中是至关重要的。促炎性分子的表达较低指示较小的炎症,而表达较高指示增大的炎症状态。根据毒性和病理学损害,所产生的TNF- α (肿瘤坏死因子)将大大刺激粘附分子和细胞因子(例如E-选择素、ICAM-1和白介素8(IL-8))的表达。粘附分子和细胞因子表达增加通过向炎症位点补充白细胞(炎性细胞渗透通过局部血管内皮)介导免疫和炎性应答。

[0010] 之前的研究显示,与对照相比,在晚期乳腺癌患者中,可溶性E-选择素和ICAM-1的水平显著地更高。此外,粘附分子水平升高预示存活减少。另外,各种促炎性介质可能不仅开启倾向于肿瘤的炎性血管生成,一种基本由血管内皮生长因子控制的过程,还促进肿瘤转移。

[0011] 因此,为了减少有害炎症,关键在于限制这些促炎性分子的合成,以便减少异常的炎性应答。

[0012] 我们的研究显示,在分子水平,包含后文提及的成分的组合物是抗炎性剂,能够减少TNF α 诱导的粘附分子ICAM-1和E-选择素在HUVEC(人脐静脉内皮细胞)上的表达,以及细胞因子IL-8表达。这样的抗炎性潜力导致抑制肿瘤进展和较小肿瘤尺寸(见以上章节和实施例中的数据,所述数据自体外和体内研究获得)。因此,包含后文提及的成分的组合物提供抗炎性效果以支持管理癌症和治疗癌症并存病。

[0013] 在随机实验中,将包含后文提及的成分的组合物皮下注射入小鼠癌症模型。观察到,与非治疗小鼠相比,所述组合物抑制治疗的小鼠中的肿瘤生长和肿瘤尺寸(见实施例2中的数据,获得自体外和体内研究)。

[0014] 癌症患者将包含后文提及的成分的组合物用于局部配制物中,以阻止化疗诱导的秃头症。一些患者报告,除了对不想要的脱发的有益效果之外,他们患有的其它症状,如疲劳,开始稳定地改善。

发明内容

[0015] 患有肝癌的患者口服施用包含后文提及的成分的组合物。基于内科医生和患者的报告和摄入所述组合物之前和之后拍摄的照片,他的一般状况开始显著改善,包括癌症相关的疲劳的缓和。

[0016] 通过口服途径、局部或胃肠外途径、肿瘤内注射或其组合施用含有葱属物种提取物、柑橘属物种提取物、泡林藤属物种提取物和可可属物种提取物作为活性成分的组合物,所述葱属物种提取物含有槲皮素,发现所述施用对于管理癌症和治疗癌症并存病具有新的且之前位置的效果。

[0017] 本发明建议一种用于管理癌症和治疗癌症并存病的方法,所述癌症并存病包括但不限于癌症相关的疲劳、恶病质、厌食、疼痛、贫血、虚弱、抑郁、肌无力、恶心、呕吐、皮肤和皮肤附属结构不良反应,所述方法包括施用含有葱属物种提取物、柑橘属物种提取物、泡林藤属物种提取物和可可属物种提取物作为活性成分的组合物,所述葱属物种提取物含有槲皮素,所述组合物通过常规和非常规途径,和/或作为细胞疗法中的辅助增效剂,或局部途径,或胃肠外途径,或肿瘤内注射,或其组合而施用。

附图说明

[0018] 图1对应在不同时间测量的平均体重(克)的曲线。

[0019] 图2对应在不同时间测量的平均肿瘤体积(mm³)的曲线。

[0020] 发明详述

[0021] 特别地,本发明涉及一种用于管理癌症和治疗癌症并存病的方法,所述癌症并存病包括但不限于癌症相关的疲劳、恶病质、厌食、疼痛、贫血、虚弱、抑郁、认知功能受损、食欲不振、肌无力、恶心、呕吐、关节炎、器官损伤(包括但不限于放射诱导的烧伤、化疗和放疗的心脏毒性导致的心脏病)、高血压、血栓栓塞、偶发性胸痛、呼吸困难、呼吸短促、头晕、昏厥、苍白(苍白的皮肤和嘴唇)、头痛、难以集中注意力、失眠、难以保暖、流血问题、指甲损伤和皮肤附属结构不良反应,例如皮肤刺激和干燥、痛性和干燥性口腔溃疡,所述方法包括通过口服途径、局部或胃肠外途径、肿瘤内注射或其组合施用含有葱属物种提取物、柑橘属物种提取物、泡林藤属物种提取物和可可属物种提取物作为活性成分的组合,所述葱属物种提取物含有槲皮素。

[0022] 在管理癌症和治疗癌症并存病的方法中,根据本发明,特别感兴趣的那些是这样的方法,其中基于四种活性成分的总重量,优选的口服组合物组合物含有30%至93%重量百分比的葱属物种提取物、3%至33%重量百分比的柑橘属物种提取物、0.10%至2.5%重量百分比的泡林藤属物种提取物(粉化或未粉化)和0.10%至2.5%重量百分比的可可属物种提取物(粉化或未粉化),所述葱属物种提取物含有槲皮素。

[0023] 根据实施方案,基于四种活性成分的总重量,所述组合物包含30%至93%重量百分比的葱属物种提取物、3%至33%重量百分比的柑橘属物种提取物、0.10%至2.5%重量百分比的泡林藤属物种提取物(粉化或未粉化)、0.10%至2.5%重量百分比的可可属物种提取物(粉化或未粉化)、0.5%至3.0%重量百分比的氯化钠和25%至50%重量百分比的甘油,所述葱属物种提取物含有槲皮素。

[0024] 在管理癌症和治疗癌症并存病的方法中,更优选的那些是这样的方法,其中所述组合物不仅用作常规口服组合物、用于注射的组合物、局部应用,还用作辅助增效剂用于管理癌症和治疗相关的并存病。基于四种活性成分的总重量,所述组合物含有30%至93%重量百分比的葱属物种提取物、3%至33%重量百分比的柑橘属物种提取物、0.10%至2.5%重量百分比的泡林藤属物种提取物(粉化或未粉化)和0.10%至2.5%重量百分比的可可属物种提取物(粉化或未粉化),所述葱属物种提取物含有槲皮素。

[0025] 根据实施方案,基于四种活性成分的总重量,所述组合物含有30%至93%重量百分比的洋葱(*Allium cepa*)提取物、3%至33%重量百分比的柠檬(*Citrus lemon*)提取物、0.10%至2.5%重量百分比的泡林藤属物种提取物(粉化或未粉化)和0.10%至2.5%重量百分比的可可属物种提取物(粉化或未粉化)。

[0026] 根据实施方案,基于四种活性成分的总重量,所述组合物包含30%至93%重量百分比的葱属物种提取物、3%至33%重量百分比的柑橘属物种提取物、0.10%至2.5%重量百分比的泡林藤属物种提取物(粉化或未粉化)、0.10%至2.5%重量百分比的可可属物种提取物(粉化或未粉化)、0.5%至3.0%重量百分比的氯化钠和25%至50%重量百分比的甘油,所述葱属物种提取物含有槲皮素。

[0027] 术语葱属物种提取物具体指从葱属(百合科)的所有物种特别是洋葱获得的提取物和天然提取物,其可能含有槲皮素。术语柑橘属物种提取物具体指从柑橘属(芸香科)的所有物种特别是柠檬获得的提取物和天然提取物。术语泡林藤属物种提取物(粉化或未粉化)具体指从泡林藤属(无患子科)的所有物种特别是瓜拿纳(*Paullinia cupana*)获得的提取物和天然提取物。术语可可属物种提取物(粉化或未粉化)具体指从可可属(锦葵科)的所有物种特别是可可(*Theobroma cacao*)获得的提取物和天然提取物。

[0028] 根据本发明,所用的最优选的组合是那些基于四种活性成分的总重量,含有约87%重量百分比的洋葱提取物、约12%重量百分比的柠檬提取物、约0.5%重量百分比的瓜拿纳提取物(粉化或未粉化)和约0.5%重量百分比的可可提取物(粉化或未粉化)的组合,所述洋葱提取物含有槲皮素。

[0029] 根据本发明,所述组合物以混合物的形式长期施用,所述混合物含有葱属物种提取物、柑橘属物种提取物、泡林藤属物种提取物和可可属物种提取物作为活性成分,所述葱属物种提取物含有槲皮素。

[0030] 根据本发明的实施方案,所述组合物在数月或更长的时期中每日施用,所述组合物含有葱属物种提取物、柑橘属物种提取物、泡林藤属物种提取物和可可属物种提取物作为活性成分,所述葱属物种提取物含有槲皮素。

[0031] 为了获得对于管理癌症和治疗癌症并存病的可测量的效果,必需长期施用所述组合物,优选至少6个月。当使用根据本发明获得的组合物时,剂量可以在相当宽的范围内变化,并且必须根据所治疗的人和所关注的病症进行设置。药物组合物通常含有0.4至1000mg,优选2至400mg如上限定的活性成分,所述活性成分为干燥提取物形式。

[0032] 本发明还涉及组合物,其含有葱属物种提取物、柑橘属物种提取物、泡林藤属物种提取物和可可属物种提取物作为活性成分,所述葱属物种提取物含有槲皮素,所述组合物用于通过常规或非常规途径,和/或作为细胞疗法中的辅助增效剂,或局部途径,或胃肠外途径,或肿瘤内注射,或其组合,管理癌症和治疗癌症并存病,所述癌症并存病包括但不限于癌症相关的疲劳、恶病质、厌食、疼痛、贫血、虚弱、抑郁、肌无力、恶心、呕吐、皮肤和皮肤附属结构不良反应。

[0033] 根据本发明的实施方案,用于管理癌症和治疗癌症并存病的组合物含有葱属物种提取物、柑橘属物种提取物、泡林藤属物种提取物(粉化或未粉化)和可可属物种提取物(粉化或未粉化),所述葱属物种提取物含有槲皮素。

[0034] 根据本发明进一步的实施方案,基于四种活性成分的总重量,用于管理癌症和治疗癌症并存病的组合物含有30%至93%重量百分比的葱属物种提取物、3%至33%重量百分比的柑橘属物种提取物、0.10%至2.5%重量百分比的泡林藤属物种提取物(粉化或未粉化)和0.10%至2.5%重量百分比的可可属物种提取物(粉化或未粉化),所述葱属物种提取物含有槲皮素。

[0035] 治疗的实施例

[0036] 患者每天通过口服、局部、胃肠外途径或肿瘤内注射(单独或组合)接受治疗,所述治疗含有:

- [0037] - 洋葱提取物(含有槲皮素): 87.04 %
 - 柠檬提取物: 11.96 %
 - 瓜拿纳提取物: 0.50 %
 - 可可提取物: 0.50 %

[0038] (此后称为组合物A)。

[0039] 如专利申请WO 2008/113912的实施例1中所说明的制备此涂剂(lotion)。

[0040] 组合物A是四种天然成分的混合物,据报道对异常细胞凋亡以及炎症过程中的缺陷有益影响。这说明组合物A能够在管理上文提到的癌症和癌症治疗相关的并存病中有积极影响。

[0041] 实施例1:通过抑制TNF α -诱导的促炎性分子ICAM-1、E选择素和白介素8的表达(如表2a、2b和2c所总结),研究含有葱属物种提取物、柑橘属物种提取物、泡林藤属物种提取物和可可属物种提取物作为活性成分的组组合物的抗炎性作用,所述葱属物种提取物含有槲皮素。

[0042] 表1:所测试的组合物

组合物	成分	总 %wt
A	洋葱	50.0
	柑橘属	50.0
B	洋葱	87.5
	柑橘属	12.5
C	洋葱	87.0
	柑橘属	12.0
	瓜拿纳干燥提取物	0.5
	可可干燥提取物	0.5
对照	培养基	

[0044] 表2a.“组合物”对粘附分子ICAM-1(CD54)在内皮细胞(HUVECs)表面上的表达的影响

[0045]

组合物	通过 sABC*测量的 的非处理细胞	通过 sABC*测量的 的 TNF 处理的细胞	与对照相比的 % 增加 (+) % 减少 (-)
培养基(对照)	3 172	386 181	
A	2 061	296 561	-23%
B	1 947	297 444	-23%
C	1 664	254 171	-34%

[0046] *每细胞结合的特异性抗体

[0047] 表2b.“组合物”对粘附分子E-选择素/ELAM-1(CD62E)在内皮细胞(HUVECs)表面上的表达的影响

	组合物	通过 sABC*测量的 的非处理细胞	通过 sABC*测 量的 TNF 处理 的细胞	与对照相比的 % 增加 (+) % 减少 (-)
[0048]	培养基(对照)	不可测	3 074	
	A	251	4 235	+38%
	B	186	3 447	+12%
	C	65	1 648	-46%

[0049] *每细胞结合的特异性抗体

[0050] 表2c. “组合物”对细胞因子白介素8(IL-8)在内皮细胞(HUVECs)表面上的表达的影响

	组合物	通过 sABC*测量的 的非处理细胞	通过 sABC*测 量的 TNF 处理 的细胞	与对照相比的 % 增加 (+) % 减少 (-)
[0051]	培养基(对照)	1 164	5 406	
	A	1 067	6 274	+16%
	B	1 015	5 563	+3%
	C	887	4 827	-11%

[0052] *每细胞结合的特异性抗体

[0053] 实施例2:使用携带皮下人类KB类肿瘤的裸鼠研究新的“组合物”的抗肿瘤活性

[0054] 图1是具有皮下人类KB类肿瘤的裸鼠的平均体重曲线。小鼠在第7天随机化,并分别接受每天注射100 μ l,0.3%和1%的组合物溶液(THI),连续注射5天。

[0055] 在图1中,x轴代表时间(天);y轴代表裸鼠的平均体重(g)。蓝色(曲线2):对照运载工具;粉色(曲线3):0.3%的组合物(THI);黄色(曲线1):1%的组合物(THI)。未观察到显著的体重改变。

[0056] 图2是具有皮下人类KB类肿瘤的裸鼠的平均肿瘤体积曲线。小鼠在第7天随机化,并分别接受每天注射100 μ l,0.3%和1%的组合物溶液(THI),连续注射5天。

[0057] 在图2中,x轴代表时间(天);y轴代表裸鼠的平均肿瘤体积(mm³)。蓝色(曲线2):对照运载工具;粉色(曲线3):0.3%的组合物(THI);黄色(曲线1):1%的组合物(THI)。未观察到显著的体重改变。0.3%的组合物(THI)与对照相比,显示抗肿瘤作用。

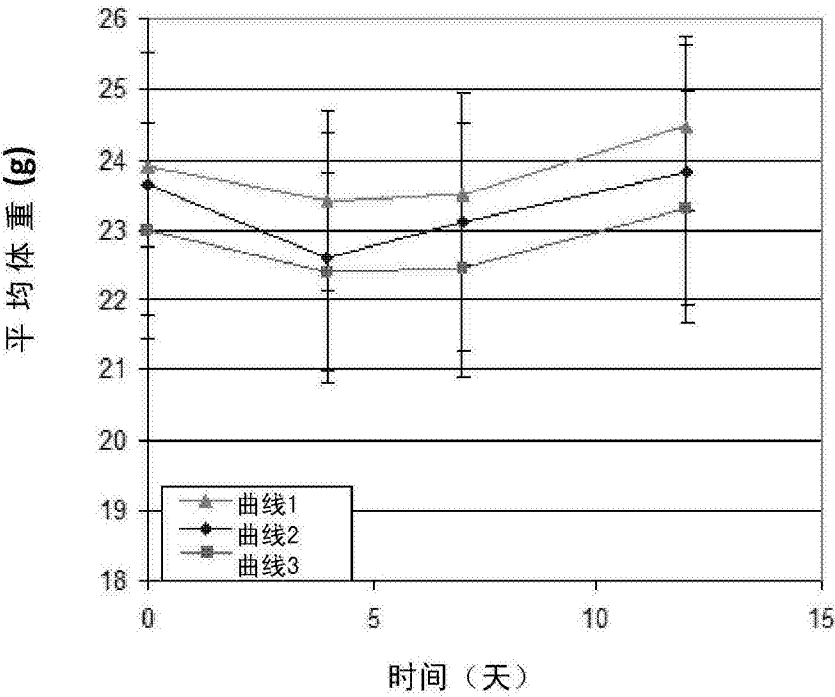


图1

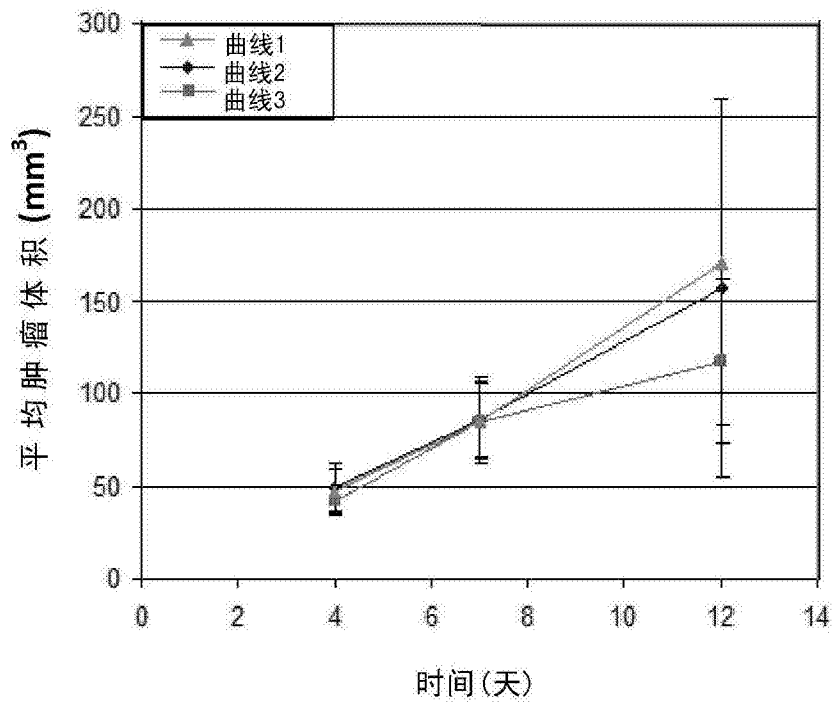


图2