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(54) Title: PROCESS FOR THE LARGE SCALE PRODUCTION OF FRUIT CELLS AND TREATMENT OF DISEASES WITH
SUCH CELLS

(57) Abstract: The disclosure provides a method for treating, reducing, alleviating or preventing metabolic syndrome or metabolic
malady, comprising administering a composition comprising a cell line callus culture of fruit cells grown in vitro. Further provided
are fruit cells prepared according to a large scale process. The cell line callus culture of grape berry cells manufactured according to
the process includes resveratrol in an amount of at least 1000 mg/kg powder.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL 13/51052

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 63/00; A61K 8/97; C12Q 1/02; A01H 9/00 (2014.01)

USPC - 424/93.7; 424/725; 435/29; 800/295

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)

IPC(8) - A01N 63/00; A61K 8/97; C12Q 1/02; A01H 9/00 (2014.01)

USPC - 424/93.7; 424/725; 435/29; 800/295; 424/93.1

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

IPC(8) - A01N 63/00; A61K 8/97; C12Q 1/02; A01H 9/00 (2014.01) - see keyword below

USPC - 424/93.7; 424/725; 435/29; 800/295; 424/93.1 - see keyword below

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

PubWEST(USPT,PGPB,EPAB,JPAB); PatBase; Medline, Google: grape berry, fruit, culture, cross section, skin, flesh, seed, embryo, seeded, seedless, cultivars, coat, hypertension, hypertriglyceridemia, diabetes, endothelium, Endothelial, inflammation, hypersensitivity, atherosclerosis, nutraceutical, coronary heart disease, blood pressure, mouthwash

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 8,216,801 B2 (ESHDAT et al.) 10 July 2012 (10.07.2012), Abstract; col 1, ln 32-46; col 4, ln 3-6, 8-10, and 34-35; col 5, ln 25-26; col 7, ln 58-67; col 8, ln 13-15; col 9, ln 52; col 16, ln 16, 24-27, and 37-40; col 17, ln 1-6, and 9-67; col 18, ln 1-10; and claims 1, 8, 15, and 22	1-9, 27 ----- 30
Y	SEYMOUR et al. Whole Grape Intake Impacts Cardiac Peroxisome Proliferator-Activated Receptor and Nuclear Factor B Activity and Cytokine Expression in Rats With Diastolic Dysfunction. Hypertension. 2010, Vol. 55(5), p. 1179-85. Abstract; and pg 1182, col 2, para 2	30
A	SATOH et al. Purified Eicosapentaenoic Acid Reduces Small Dense LDL, Remnant Lipoprotein Particles, and C-Reactive Protein in Metabolic Syndrome. Diabetes Care. 2007, Vol. 30(1), p. 144-6. Abstract; and pg 145, col 3, top para	1-9, 27, 30

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL 13/51052

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

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.: 10-23
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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, claims 1-9, 24-25, 27, 30, drawn to a method for treating, reducing, alleviating or preventing metabolic syndrome or an inflammation disorder, comprising administering a composition comprising a cell line callus culture of fruit cells grown in vitro. The first invention is restricted to wherein the fruit cells are grape berry cells, and wherein the composition is a nutraceutical composition. It is believed that claims 1-9, 27, 30 read on this first named invention. Applicants must indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be: wherein the cell line callus culture of fruit cells prepared according to a large scale process comprising growing fruit cells in a flask; inoculating the fruit cells from the flask into a first bioreactor (claims 24-25).

*****Continued in the extra sheet*****

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 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.: 1-9, 27, 30

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.

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Continuation of:
Box No III (unity of invention is lacking)

Group II, claims 28-29, drawn to a composition in a form of a powder comprising a cell line callus culture of grape berry cells grown in vitro in a large scale up process.

The inventions listed as Groups I+-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Feature

Groups I+-II are related as a product (Group II) and methods of using the product (Group I+). Among Groups I+, claims 24-25 of Groups I+ include the special technical feature of method of preparing fruit cells (method of making a product), not required by claims 1-9, 27, and 30 of Groups I+; and claims 1-9, 27, and 30 of Groups I+ are directed to the specific feature of wherein the fruit cells are grape berry cells, and wherein the composition is a nutraceutical composition, not required by claims 24-25 of Groups I+.

Common Technical Features

The inventions of Groups I+-II share the technical feature of a composition comprising a cell line callus culture of fruit cells grown in vitro; claims 2 and 6 of Groups I+ and Group II further share the technical feature of wherein the fruit cells are grape-berry cells, and wherein cell line callus culture of grape berry cells is derived from one or more of grape-berry cross section, grape-berry skin, grape-berry flesh, grape seed, grape embryo of seeded or seedless cultivars or grape seed coat; and claims 24-25 of Groups I+ and Group II further share the technical feature of wherein cell line callus culture of fruit cells prepared according to a large scale process (Group II - a large scale up process).

The inventions of Groups I+ further share the technical feature of a method for treating, reducing, alleviating or preventing metabolic syndrome or metabolic malady, or an inflammation, comprising administering a composition comprising a cell line callus culture of fruit cells grown in vitro.

However, these shared technical features do not represent a contribution over prior art as being anticipated by US 8,216,801 B2 to ESHDAT et al. (hereinafter 'Eshdat') as follows:

Eshdat discloses a method for treating, reducing, alleviating or preventing inflammation (Abstract - 'methods of treating an inflammatory disorder in a subject'), ---comprising administering a composition comprising a cell line callus culture of fruit cells grown in vitro (Abstract - 'administering to the subject ...a pharmaceutical composition including a fruit, for example a grape,... cultured fruit cells'; claim 1 - 'treating inflammation in a subject, ... administering ... composition consisting ... cell line callus culture of grape berry cells grown in vitro'). Eshdat further discloses wherein the inflammation disorder is characterized by vascular endothelium dysfunction (Abstract) including atherosclerosis (col 5, ln 25-26 - 'the inflammatory disease is atherosclerosis').

Although Eshdat does not expressly teach using the method for treating, reducing, alleviating or preventing metabolic syndrome or metabolic malady, this limitation is encompassed by the disclosure of Eshdat, because treating vascular endothelium dysfunction including atherosclerosis encompasses treating, reducing, alleviating or preventing metabolic syndrome or metabolic malady, because atherosclerosis development is associated with elevated LDL levels and accumulation of lipoproteins (col 1, ln 32-46 - 'atherosclerosis development,... endothelial dysfunction, plaque formation, ...Endothelial dysfunction...as a result of exposure to cardiovascular risk factors... elevated LDL levels,... mediating accumulation of ...lipoproteins within the wall'), both of which are features in metabolic syndrome, and metabolic syndrome is a precursor of cardiovascular disorder (Please see Satoh et al.: Abstract - 'particles and small dense LDL (sdLDL), which are newly recognized risk factors for cardiovascular disease (CVD)...atherogenic sdLDL particles and remnant lipoprotein particles in the metabolic syndrome, a precursor of CVD').

Eshdat further discloses wherein the fruit cells are grape-berry cells (claim 1 - 'cell line callus culture of grape berry cells grown in vitro'), and wherein cell line callus culture of grape berry cells is derived from one or more of grape-berry cross section, grape-berry skin, grape-berry flesh, grape seed, grape embryo of seeded or seedless cultivars or grape seed coat (claim 1 - 'the cell line callus culture of grape berry cells is derived from one or more of grape-berry cross section, grape-berry skin, grape-berry flesh, grape seed, grape embryo of seeded or seedless cultivars or grape seed coat'); as well as ---wherein cell line callus culture of fruit cells prepared according to a large scale process (claim 1; col 10, ln 64 to col 11, ln 15 - 'Preparations may be derived from fresh or frozen fruit cell cultures using any method known in the art ...The preparation may comprise all the culture ... may include large scale maceration').

Without a shared special technical feature, the inventions lack unity with one another.

Groups I+-II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note re item 4: Claims 10-23 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.

*****Continued in the next extra sheet*****

INTERNATIONAL SEARCH REPORT

International application No.

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Continuation of:

The previous extra sheet - Box No III (unity of invention is lacking)

Note:

I) Claim 5 is objected to as using an improper alternative claim limitation. It is assumed that the limitation "is hypertension, hypertriglyceridemia and diabetes" is read as "is hypertension, hypertriglyceridemia or diabetes". For the purposes of this ISR, claim 5 is construed as follows:

5. The method of any one of claims 3 and 4, wherein the one or more conditions is hypertension, hypertriglyceridemia or diabetes.

II) Claim 6 is objected to as lacking a proper antecedent basis for the "the cell line callus culture of grape berry cells" limitation. It is assumed that claim 6 depends upon claim 2.

III) Claims 8-9 are objected to as lacking a proper antecedent basis for the "the nutraceutical composition" limitation. It is assumed that claims 8-9 depend upon claim 7.

IV) Claim 26 is missing from the application.