(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 December 2011 (01.12.2011)

PCT

(10) International Publication Number
WO 2011/147012 A1

(51) International Patent Classification:
A61K 31/79 (2006.01) *A61K 31/593* (2006.01)
A61K 31/194 (2006.01) *A61K 36/185* (2006.01)
A61K 31/365 (2006.01) *A61K 36/28* (2006.01)
A61K 31/404 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/CA2010/000817

(22) International Filing Date:
26 May 2010 (26.05.2010)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **FEM MED FORMULAS LIMITED PARTNERSHIP** [CA/CA]; 64 Bakersfield Street, Toronto, Ontario M3J 2W7 (CA).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **COVENTRY, Krista** [CA/CA]; 60 Wyndham Suite South, Suite 604, Guelph, Ontario N1E 7H7 (CA).

(74) Agents: **NORTON ROSE OR LLP/S.E.N.C.R.L., s.r.l.** et al.; Suite 2500, 1 Place Ville Marie, Montreal, Québec H3B 1R1 (CA).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2011/147012 A1

(54) Title: COMPOSITIONS COMPRISING BOTANICALS, INCLUDING THE USE AND METHOD OF USE THEREOF

(57) Abstract: A composition comprising_indole-3-carbinol, milk thistle, schizandra, stinging nettle, hydroxymatairesinol ligands and optionally calcium-d- glucarate and 400 KJ Vitamin D for altering urinaπ estrone metabolite and pre\enting breast cancer in pre and post menopausal women

COMPOSITIONS COMPRISING BOTANICALS, INCLUDING THE USE AND METHOD OF USE THEREOF

FIELD

The present invention relates to compositions comprising botanicals, the use and the method of use thereof, and in particular compositions comprising indole-3-carbinol for altering urinary estrone metabolite levels and preventing breast cancer in women.

BACKGROUND

As health care costs for disease treatments continue to soar – science, industry, healthcare systems and health care practitioners continue to search for those products which will best serve the preventative model to reduce treatments costs, and provide individuals with healthy and safe products which produce positive health outcomes. According to health statistics from Statistics Canada and the U.S. Department of Health, breast cancer is the most common cancer among women. Over her lifetime, one in nine women will be diagnosed with breast cancer, and one in twenty-seven will die from it. The majority of breast cancers are estrogen-dependent, so maintaining a healthy estrogen balance will reduce breast cancer risk.

Studies have found that two specific metabolites of estrogen metabolism affect breast cancer susceptibility. As urinary levels of 2-hydroxyestrone (2-OHE) increase and levels of 16-αhydroxyestrone decrease (16-αOHE), the risk for breast cancer decreases, because 16-αOHE is an independent risk factor for breast cancer. In most human trials, results are presented as a ratio of urinary 2-OHE to urinary 16-αOHE, and the higher the ratio, the better, in terms of breast health. The optimal urinary ratio of 2-OHE to 16αOHE is 2:1, while a 1:1 ratio is associated with increased breast cancer risk. This ratio is commonly referred to as the estrogen metabolite ratio (EMR).

In a prospective study by Muti et al. (2000), 10,786 Italian women were followed for 5.5 years, and the EMR was measured at baseline in all of these women. The number of diagnosed breast cancer cases that developed during the study period was compared with baseline EMRs. In premenopausal women, those with the higher ratio had, on average, an odds ratio for breast cancer of 0.58, compared to those with a lower ratio. This means that their risk of developing breast cancer was just over half that of the lower ratio group – i.e. the women with a optimal ratio had approximately 50% less risk than those with a sub-optimal ratio. In a case-control U.S. trial (breast cancer cases, compared to matched non-breast cancer controls) published by Kabat et al. (1997) in post-menopausal there was a strong inverse relationship between EMR and breast cancer, and a strong positive relationship between 16-αOHE and breast cancer. This means that the higher the ratio, the lower the breast cancer incidence, and the higher the level of 16-αOHE, the higher the incidence. The authors of a U.K.-based prospective trial reported that post-menopausal women who developed breast cancer over the 8 years of the trial had, on average, a 15% lower EMR than matched controls. Also, women whose ratio was in the highest third had a 30% lower risk of breast cancer development than those in the lower two-thirds EMR (Meilahn et al., 1998).

Indole-3-carbinol (I3C) helps maintain healthy estrogen levels in the body by balancing estrogen metabolites. It does this by shifting the pathway by which estrogens are metabolized. Estradiol undergoes initial oxidative conversion to estrone. Estrone and estradiol can undergo hydroxylation by different cytochrome p450 isoenzymes. Hydroxylation occurs either in the 2 or 16 carbon.

These different metabolites have opposing effects on estrogen receptor-positive breast cancer cells. 16-αOHE stimulates proliferation, while 2-OHE shows no effect on cell growth. Human studies have shown that I3C can shift the balance of estrogen metabolites in the body from 16-αOHE to 2-OHE.

In one human trial, 17 of 20 women (85%) supplemented with 200 or 400 mg/day I3C sustained an average increase of 44% in the ratio of 2-OHE to 16-αOHE over the course of the trial. In another human trial, the 2-OHE:16-αOHE ratio in four out of five

obese women who were supplemented with I3C were increased, on average, by 93% over a two-month period. In the same trial, this ratio in non-obese women increased by an average of 38%. In a third human trial, all 20 women who consumed 300 or 400 mg of I3C for a period of 4 weeks significantly increased this ratio. A fourth study reported that in 20 women consuming 400 mg I3C daily, the average increase in the 2-OHE:16-αOHE ratio was 65%. Overall, supplementation with 200-400 mg IC3 appears to increase this critical ratio by approx. 60% in the vast majority of women who consume it on a regular basis.

SUMMARY OF INVENTION

In one aspect, there is provided a composition for altering urinary estrone metabolite levels, wherein the composition comprises: Indole-3-Carbinol; Milk Thistle (*Silybum marianum* seed extract, 2:1); Schizandra (*Schisandra chinensis* fruit extract, 4:1); Stinging Nettle (*Urtica dioica* leaf extract, 4:1); and Hydroxymatairesinol Lignans (*Picea abies* [Norway Spruce]).

In another aspect, the composition is provided for preventing breast cancer in a woman.

There is also provided a use of a composition comprising Indole-3-Carbinol, Milk Thistle (*Silybum marianum* seed extract, 2:1), Schizandra (*Schisandra chinensis* fruit extract, 4:1), Stinging Nettle (*Urtica dioica* leaf extract, 4:1), and Hydroxymatairesinol Lignans (*Picea abies* [Norway Spruce]) for altering urinary estrone levels.

In an alternate aspect, a use of the composition is provided for preventing breast cancer in a woman.

There is further provided a method of use of a composition comprising Indole-3-Carbinol, Milk Thistle (*Silybum marianum* seed extract, 2:1), Schizandra (*Schisandra chinensis* fruit extract, 4:1), Stinging Nettle (*Urtica dioica* leaf extract, 4:1), and Hydroxymatairesinol Lignans (*Picea abies* [Norway Spruce]) for altering urinary

estrone levels wherein a therapeutically effective dose of the composition is administered to a woman twice daily.

In another aspect, a method of use of the composition is provided for preventing breast cancer wherein a therapeutically effective dose of the composition is administered to a woman twice daily.

DETAILED DESCRIPTION

There is described herein a unique composition that is specifically designed and intended to reduce the risk of breast cancer by increasing and optimizing the EMR.

In one embodiment, there is provided a composition for altering urinary estrone metabolite levels in a woman, wherein the composition comprises: Indole-3-Carbinol; Milk Thistle (*Silybum marianum* seed extract, 2:1); Schizandra (*Schisandra chinensis* fruit extract, 4:1); Stinging Nettle (*Urtica dioica* leaf extract, 4:1); and Hydroxymatairesinol Lignans (*Picea abies* [Norway Spruce]). In a preferred embodiment, the composition further comprises Vitamin D (Cholecalciferol [Vitamin D3]) and/or Calcium-D-Glucarate.

In a further aspect, the composition for altering urinary estrone metabolite levels in a woman comprises: about 200 mg of Indole-3-Carbinol; about 100 mg of Milk Thistle (*Silybum marianum* seed extract, 2:1); about 75 mg of Schizandra (*Schisandra chinensis* fruit extract, 4:1); about 50 mg of Stinging Nettle (*Urtica dioica* leaf extract, 4:1); and about 10 mg of Hydroxymatairesinol Lignans (*Picea abies* [Norway Spruce]). Preferably, the composition further comprises about 400 IU/10 mcg of Vitamin D (Cholecalciferol [Vitamin D3]) and/or about 75 mg of Calcium-D-Glucarate.

In another embodiment, there is provided a composition for preventing breast cancer in a woman, wherein the composition comprises: Indole-3-Carbinol; Milk Thistle (*Silybum marianum* seed extract, 2:1); Schizandra (*Schisandra chinensis* fruit extract, 4:1); Stinging Nettle (*Urtica dioica* leaf extract, 4:1); and Hydroxymatairesinol Lignans

(*Picea abies* [Norway Spruce]). In a preferred embodiment, the composition further comprises Vitamin D (Cholecalciferol [Vitamin D3]) and/or Calcium-D-Glucarate.

In a further aspect, the composition for preventing breast cancer in a woman comprises: about 200 mg of Indole-3-Carbinol; about 100 mg of Milk Thistle (*Silybum marianum* seed extract, 2:1); about 75 mg of Schizandra (*Schisandra chinensis* fruit extract, 4:1); about 50 mg of Stinging Nettle (*Urtica dioica* leaf extract, 4:1); and about 10 mg of Hydroxymatairesinol Lignans (*Picea abies* [Norway Spruce]). Preferably, the composition further comprises about 400 IU/10 mcg of Vitamin D (Cholecalciferol [Vitamin D3]) and/or about 75 mg of Calcium-D-Glucarate.

In another embodiment, the use of a composition comprising Indole-3-Carbinol, Milk Thistle (*Silybum marianum* seed extract, 2:1), Schizandra (*Schisandra chinensis* fruit extract, 4:1), Stinging Nettle (*Urtica dioica* leaf extract, 4:1), and Hydroxymatairesinol Lignans (*Picea abies* [Norway Spruce]) is provided for altering urinary estrone levels. In preferred embodiments the composition further comprises Vitamin D (Cholecalciferol [Vitamin D3]) and/or Calcium-D-Glucarate.

The use of a composition for altering urinary estrone levels increases the ratio of 2-hydroxyestrone relative to 16-αhydroxyestrone. Preferably, the ratio of 2-hydroxyestrone relative to 16-αhydroxyestrone is about 2:1.

In another embodiment, a composition comprising Indole-3-Carbinol, Milk Thistle (*Silybum marianum* seed extract, 2:1), Schizandra (*Schisandra chinensis* fruit extract, 4:1), Stinging Nettle (*Urtica dioica* leaf extract, 4:1), and Hydroxymatairesinol Lignans (*Picea abies* [Norway Spruce]) is provided for use in preventing breast cancer in a woman. In preferred embodiments the composition further comprises about 400 IU/10 mcg of Vitamin D (Cholecalciferol [Vitamin D3]) and/or about 75 mg of Calcium-D-Glucarate.

The use of the composition for preventing breast cancer is preferably administered to both pre- or post-menopausal women.

In another embodiment, a method is provided for altering urinary estrone metabolite levels in a woman comprising administering to the woman a therapeutically effective amount of a composition comprising Indole-3-Carbinol, Milk Thistle (*Silybum marianum* seed extract, 2:1), Schizandra (*Schisandra chinensis* fruit extract, 4:1), Stinging Nettle (*Urtica dioica* leaf extract, 4:1), and Hydroxymatairesinol Lignans (*Picea abies* [Norway Spruce]) twice a day. In a preferred embodiment, the composition further comprises Vitamin D (Cholecalciferol [Vitamin D3]) and/or Calcium-D-Glucarate.

In some embodiments, a method is provided for preventing breast cancer in a woman comprising administering to the woman a therapeutically effective amount of a composition comprising Indole-3-Carbinol, Milk Thistle (*Silybum marianum* seed extract, 2:1), Schizandra (*Schisandra chinensis* fruit extract, 4:1), Stinging Nettle (*Urtica dioica* leaf extract, 4:1), and Hydroxymatairesinol Lignans (*Picea abies* [Norway Spruce]) twice a day. In a preferred embodiment, the composition further comprises Vitamin D (Cholecalciferol [Vitamin D3]) and/or Calcium-D-Glucarate.

Advantageously, the use of a composition of the present invention may also have clinical utility as a preventative tool. Clinicians such as General Practitioners, Naturopathic Doctors and Registered Dieticians may use a composition of the present invention to conduct a 'Measure-Treat-Measure' program using a composition of the present invention as the 'Treat' and urinary estrogen metabolite testing as the 'Measure' to capture the risk reduction factors for a woman's preventative breast health. This risk reduction factor is captured within about 30 days of supplementation based on the biomarker, the treatment influences and the risk reduction associated with the improvement of the biomarker.

The following example is illustrative of various aspects of the invention, and does not limit the broad aspects of the invention as disclosed herein.

EXAMPLE

Example 1

A double blind placebo controlled parallel clinical trial has been conducted to demonstrate the safety, efficacy and positive health outcomes of an embodiment of the present invention consisting of five botanicals including indole-3-carbinol, Schisandra chinesis, Milk thistle, Stinging nettle, and HMR lignans, in addition to vitamin D and calcium-D-glucarate for the alteration of urinary estrone metabolite levels in both pre- and post-menopausal women, with or without Hormone Replacement Therapy.

Pilot Trial Results

Preliminary reports from the clinical trial investigating a composition of the present invention resulted in significant improvement in the EMR. Both pre- and post-menopausal women using the composition had similar effects compared to baseline and to the placebo, showing that the product exhibits positive outcomes and risk reduction factors across the demographic spectrum of women's breast health.

Stage One findings on a combined group of pre- and post- menopausal women from the clinical trial investigation has demonstrated statistical significance in these women as a combined group. This statistical significance demonstrates that the composition of the invention is capable of bringing women into the optimal ratio for breast cancer prevention purposes within 30 days and will allow for optimal publication potential.

In addition to the positive outcomes recorded in the pilot trial and completion of Stage One, trial participants had no serious adverse events.

Time-Lines

The trial commenced on Day 0, and recruitment of the first 25 subjects (pre- and post-menopausal women not taking hormones) was completed by Day 18. Completion of sample collection for the 25th recruited subject took place on Day 50. Blood and urine

samples were delivered to the testing lab by Day 53, and analysis of blood and urine samples took place over the following 4 weeks. Results were received on Day 80.

On Day 228, a second batch of blood and urine samples were tested. This batch included pre-menopausal women from subject #20 to subject #40, and post-menopausal women from subject #8 to subject #28. The urinary estrogen metabolite results from this group are now available. These results have been combined with the results from the previous group of subjects.

Results

In an analysis of the whole data (i.e. pre- and post-menopausal data combined), there was a statistically significant difference in the 2-OHE:16-OHE ratio between the supplement group and the placebo group.

The urinary estrone metabolite data for pre- and post-menopausal women were analysed separately. Because some of the estrogen metabolites of interest were either absent from the urine, or present at undetectable levels (see previous progress report), data for 4 pre-menopausal women (subjects 08, 09, 018 and 019) and 8 post-menopausal women (subjects 01, 02, 05, 06, 07, 12, 013 and 014) was omitted. Therefore, data from 36 pre-menopausal women and 19 post-menopausal women were included for assessment. Because of the nature of the randomisation process, in which randomisation for all 144 subjects was completed, an even number of subjects in each sub-group does not occur until all subjects have been recruited and the trial is completed. Thus, there were 17 pre-menopausal women consuming the placebo and 19 consuming the treatment. In the post-menopausal group, 10 women consumed the placebo and 9 consumed the treatment.

A total sample size of 55 subjects is sufficient to detect a difference, if one is present, and this beneficial difference in the 2:16OHE ratio (the biomarker of greatest interest), in the supplement group was observed when both pre- and post-menopausal subjects' data was combined.

Analysis of enterolactone levels for the second batch of samples are being analysed and will be assessed as part of a subsequent report.

Table 1 2-hydroxyestrone levels, 16-hydroxyestrone levels and calculated 2-OH estrone:16-OH estrone levels in urine of women consuming the composition or a placebo (average values and standard deviation).

		PRE-MENOPAUSAL WOMEN N=36				POST-MENOPAUSAL WOMEN N=19				ALL WOMEN N=55			
Biomarker	Value	Supplement		Placebo		Supplement		Placebo		Supplement		Placebo	
ng/ml	Time-point>>	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
2-OH Estrone	Average	4.68	9.43	7.14	9.87	5.94	7.44	8.25	8.28	5.36	8.34	7.03	9.29
	SD	3.91	8.27	6.10	8.51	5.37	5.99	9.52	7.67	4.42	6.96	6.95	8.34
16-OH Estrone	Average	7.94	7.84	6.48	6.29	3.00	2.95	4.79	4.62	6.09	6.42	5.57	5.88
	SD	5.71	5.80	4.66	4.22	2.05	2.12	3.77	3.92	5.20	5.15	4.29	4.39
2:16-OH Ratio	Average	0.88	1.57	1.22	1.64	2.17	3.27	1.82	1.91	1.33	2.19*	1.46	1.79
	SD	0.80	1.32	0.80	0.99	1.72	3.31	1.49	1.28	1.55	2.65	1.29	1.23

p ≤0.05 p ≤0.10 *Note that for all women, the p-value for the 2:16 ratio was 0.059

The change in 2-OHE levels in subjects consuming the supplement is quite remarkable. In the pre-menopausal group, 2-OHE levels more than doubled (4.68 to 9.43), while the placebo group increased 2-OHE levels by just over one-third (7.14 to 9.87). The ratio of 2-OHE to 16-OHE showed a very similar pattern. For pre-menopausal women, the composition of the present invention appears to be increasing the 2:16 hydroxyestrone ratio much more than the placebo, i.e. the composition of the present invention almost doubled the ratio from an average of 0.88 to an average of 1.57 during the 28-day supplementation, whereas in the placebo group, this ratio rose by only one-third, from 1.22 to 1.57.

For post-menopausal women, 2-OHE levels increased by 25% (5.94 to 7.44), but did not change in the placebo group. The composition of the present invention appears to increase the 2:16 hydroxyestrone ratio in a similar manner to that of the pre-menopausal women, i.e. the composition of the present invention increased the ratio by 50%, from an average of 2.17 to an average of 3.27 during the 28-day supplementation, whereas in the placebo group, this ratio rose by only 5%, from 1.82 to 1.91. As stated previously, statistical analysis of the data (i.e. pre- and post-menopausal data combined), revealed a statistically significant difference in the 2-OHE:16-OHE ratio between the supplement group and the placebo group.

Note that the change in ratio for both the pre- and post-menopausal women consuming the supplement was almost entirely due to a significant increase in the 2-OHE levels. There was virtually no change in the 16-OHE levels.

Conclusions

From this data, and particularly from the statistically significant result of a beneficial change in the 2:16OHE ratio in the supplement group, the composition of the present invention has had a beneficial effect on the ratio of 2-hydroxyestrone to 16-hydroxyestrone, which would indicate, based on prior literature, a reduction in breast cancer risk.

Although preferred embodiments of the invention have been described herein, it will be understood by those skilled in the art that variations may be made thereto without departing from the spirit of the invention or the scope of the appended claims. All references mentioned herein are incorporated by reference in their entirety.

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CLAIMS:

1. A composition comprising: Indole-3-Carbinol; Milk Thistle; Schizandra; Stinging Nettle; and Hydroxymatairesinol Lignans.

2. The composition of claim 1 further comprising Vitamin D (Chloecalciferol [Vitamin D3]).

3. The composition of claim 1 or 2 further comprising Calcium-D-Glucarate.

4. The composition according to claim 1 comprising:
   about 200 mg of Indole-3-Carbinol;
   about 100 mg of Milk Thistle (*Silybum marianum* seed extract, 2:1);
   about 75 mg of Schizandra (*Schisandra chinensis* fruit extract, 4:1);
   about 50 mg of Stinging Nettle (*Urtica dioica* leaf extract, 4:1); and
   about 10 mg of Hydroxymatairesinol Lignans (*Picea abies* [Norway Spruce]).

5. The composition according to claim 4 further comprising about 400 IU/10 mcg of Vitamin D (Cholecalciferol [Vitamin D3]).

6. The composition according to claims 4 or 5 further comprising about 75 mg of Calcium-D-Glucarate.

7. A composition consisting of: Indole-3-Carbinol; Milk Thistle; Schizandra; Stinging Nettle; and Hydroxymatairesinol Lignans.

8. The composition according to claim 7 consisting of:
   about 200 mg of Indole-3-Carbinol;
   about 100 mg of Milk Thistle (*Silybum marianum* seed extract, 2:1);
   about 75 mg of Schizandra (*Schisandra chinensis* fruit extract, 4:1);
   about 50 mg of Stinging Nettle (*Urtica dioica* leaf extract, 4:1); and
   about 10 mg of Hydroxymatairesinol Lignans (*Picea abies* [Norway Spruce]).

9. A composition for altering urinary estrone metabolite levels in a woman, wherein the composition consists of:

200 mg of Indole-3-Carbinol;

100 mg of Milk Thistle (*Silybum marianum* seed extract, 2:1);

75 mg of Schizandra (*Schisandra chinensis* fruit extract, 4:1);

50 mg of Stinging Nettle (*Urtica dioica* leaf extract, 4:1);

10 mg of Hydroxymatairesinol Lignans (*Picea abies* [Norway Spruce]);

400 IU/10 mcg of Vitamin D (Cholecalciferol [Vitamin D3]); and

75 mg of Calcium-D-Glucarate

as medicinal ingredients.

10. The composition of claim 9 further comprising cellulose, water, microcrystalline cellulose, and magnesium stearate as non-medicinal ingredients.

11. The composition of any one of claims 1 to 10 for altering urinary estrone metabolite levels.

12. The composition of any one of claims 1 to 10 for preventing breast cancer in a woman.

13. Use of the composition of any one of claims 1 to 10 for altering urinary estrone metabolite levels.

14. Use of the composition of any one of claims 1 to 10 in the preparation of a medicament for altering urinary estrone metabolite levels.

15. The use as defined in claims 13 or 14, wherein a ratio of 2-hydroxyestrone increases relative to 16-αhydroxyestrone in urinary estrone metabolite levels.

16. The use as defined in any one of claims 13 to 15, wherein a ratio of 2-hydroxyestrone relative to 16-αhydroxyestrone is about 2:1 in urinary estrone metabolite levels.

17. Use of the composition of any one of claims 1 to 10 for preventing breast cancer in a woman.

18. Use of the composition of any one of claims 1 to 10 in the preparation of a medicament for preventing breast cancer in a woman.

19. Use of the composition of claims 17 or 18 for preventing breast cancer in a pre-menopausal woman.

20. Use of the composition of claims 17 or 18 for preventing breast cancer in a post-menopausal woman.

21. A method for altering urinary estrone metabolite levels in a woman, comprising administering to said woman a therapeutically effective amount of the composition of any one of claims 1 to 10.

22. The method of claim 21 wherein the therapeutically effective amount of the composition is administered two times daily.

23. A method for preventing breast cancer in a woman, comprising administering to said woman a therapeutically effective amount of the composition of any one of claims 1 to 10.

24. The method of claim 23 wherein the therapeutically effective amount of the composition is administered two times daily.

INTERNATIONAL SEARCH REPORT

International application No.

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 31/79*** (2006.01), ***A61K 31/194*** (2006.01), ***A61K 31/365*** (2006.01), ***A61K 31/404*** (2006.01), ***A61K 31/593*** (2006.01), ***A61K 36/185*** (2006.01), ***A61K 36/28*** (2006.01), ***A61P 35/00*** (2006.01)

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 31/79 (2006.01), ***A61K 31/194*** (2006.01), ***A61K 31/365*** (2006.01), ***A61K 31/404*** (2006.01), ***A61K 31/593*** (2006.01), ***A61K 36/185*** (2006.01), ***A61K 36/28*** (2006.01) , ***A61P 35/00*** (2006.01)

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

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

Database: EPODOC, Scopus, Internet and Canadian Patent Database

Keywords: femMed, breast health, indole-3-carbinol, milk thistle, stinging nettle, schizandra, hydroxymatairesinol lignans, estrone metabolite, hydroxyestrone and other related search terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim
X	femMED® Breast Health, Supports the Maintenance of Health Breasts, Bottle Label, Copyright 2009. [Retrieved on 04-10-2010] Retrieved from the internet: <URL:http://gnc.imageg.net/graphics/product_images/pGNC1-8107968_gnclabel_pdf.pdf> (see entire document)	1-12
X,O	Steven and Chris Program, CBC Production, Season 2, Episode 83, 10 February 2009 (10-02-2009). Retrieved from the internet: <URL:http://www.cbc.ca/video/#/Shows/Steven_and_Chris/Full_Episodes/Season_2/ID=1237706503> (see minutes 21-23 of program)	1-6 and 9-14
X	Steven and Chris Blog, Anti-Aging Foods and Supplements, Supplementary Information for the Steven and Chris Program, CBC Production, Season 2, Episode 83, 10 February 2009 (10-02-2009). Retrieved from the internet: <URL:http://www.cbc.ca/stevenandchris/2010/06/anti-aging-foods-and-supplements.html> (See item 2 under heading Broccoli)	1-6 and 9-14

[X] 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	Date of mailing of the international search report
26 January 2011 (26-11-2011)	21 February 2011 (21-02-2011)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Authorized officer Olivia Koentjoro (819) 994-1546

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/000817

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the 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] Claim Nos. : 21-24

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

Claims 21-24 are directed to a method for treatment of the human or animal body by surgery or therapy, which the International Search Authority is not required to search (Rule 39.1(iv), PCT). However, this Authority has carried out a search based on the alleged effect or purpose/use of the product defined in claims 21-24.

2. [ ] Claim 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. [ ] Claim 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 :

Please see extra sheet

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

2. [X] 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 claim 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 claim 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.

INTERNATIONAL SEARCH REPORT

International application No.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim
X	United States Clinical Trial, NCT01089049, "A Clinical Trial to Assess the Efficacy of a Supplemental Formula Targeting Breast Health in Beneficially Altering Urinary Estrogen Metabolites Levels in Both Pre- and Post-menopausal Women" 12 March 2010 (12-03-2010). [Retrieved on 04-10-2010 at www. clinicaltrials.gov] Retrieved from the internet: <URL:http://clinicaltrials.gov/ct2/show/NCT01089049?term=nct01089049&rank=1> (see entire document)	1-6 and 9-20

Continuation of Box No. III:

The international application does not comply with Rules 13.1 and 13.2 of the PCT, as it is directed to a plurality of inventive concepts that do not share a linking technical feature. The International Searching Authority has identified the following inventive concepts as follows:

Group A - Claims 1-11, 13-16 and 21-22 are directed to composition comprising indole-3-carbinol, milk thistle, schizandra, stinging nettle, hydroxymatairesinol ligands and optionally calcium-d-glucarate and 400 IU Vitamin D for altering urinary estrone metabolite; and
Group B - Claims 12, 17-20 and 23-24 are directed to a composition comprising indole-3-carbinol, milk thistle, schizandra, stinging nettle, hydroxymatairesinol ligands and optionally calcium-d-glucarate and 400 IU Vitamin D for prevention of breast cancer.

The plurality of inventive concepts arises due to the fact that the common feature of a composition comprising indole-3-carbinol, milk thistle, schizandra, stinging nettle, hydroxymatairesinol ligands and optionally calcium-d-glucarate and 400 IU Vitamin D is known in the prior art and hence cannot be considered the linking technical feature between the claims. Therefore, there is no linking technical feature between the claims of Groups A and B. The claims must be limited to one inventive concept as set out in Rule 13 of the PCT.