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(71) Applicant *(for all designated States except AG, AU, BB, CA, CY, GB, GD, GH, GM, IE, IL, IN, KE, LK, LS, MN, MW, NZ, SD, SG, SL, SZ, TT, TZ, UG, US, ZA, ZW)*: **UNILEVER N.V.** [NL/NL]; Weena 455, NL-3013 AL Rotterdam (NL).

(71) Applicant *(for AG, AU, BB, CA, CY, GB, GD, GH, GM, IE, IL, KE, LK, LS, MN, MW, NZ, SD, SG, SL, SZ, TT, TZ, UG, ZA, ZW only)*: **UNILEVER PLC** [GB/GB]; Unilever House, Blackfriars, London, Greater London EC4P 4BQ (GB).

(71) Applicant *(for IN only)*: **HINDUSTAN LEVER LTD** [IN/IN]; Hindustan Lever House, 165-166 Backbay Reclamation, Mumbai 400 020 (IN).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SCHROEDER, Fritz, H.** [NL/NL]; Erasmus Universiteit, Postbus 2040, NL-3000 CA Rotterdam (NL). **DAGNELIE, Pieter, Cornelis** [NL/NL]; Terhorst 20, NL-6262 NB Banholt (NL). **TIJBURG, Lilian, Bernadette** [NL/NL]; Rietkraag 27, NL-3121 TC Schiedam (NL). **WESTSTRATE, Jan, Adriaan** [NL/NL]; Unilever Research Vlaardingen, Olivier van Noortlaan 120, NL-3133 AT Vlaardingen (NL).

(74) Agent: **JOPPE, Hermina, L., P.**; Unilever NV, Patent Department, Olivier van Noortlaan 120, NL-3133 AT Vlaardingen (NL).

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(54) Title: COMPOSITIONS WITH ANTI-PROSTATE CANCER ACTIVITY

(57) Abstract: Compositions with anti prostate cancer activity comprise as active ingredients isoflavonoids, selenium compounds and lycopene. These compositions can be used in food supplements but also in food products.

COMPOSITIONS WITH ANTI-PROSTATE CANCER ACTIVITY

Epidemiological studies strongly suggest that the progression of prostate cancer from its focal state to its clinical state is influenced by environmental factors, however we found that dietary factors have an impact as well that is comparable to the other environmental factors or is even bigger than these.

From the literature only a few indications can be derived for the suggestion that dietary factors can have an impact on the progression of prostate cancer. This suggestion is then only disclosed for specific components but not for blends wherein different components are present and wherein the components display a synergy with respect to the inhibition of the progression of prostate cancer.

We studied whether we could find compositions comprising a blend of a number of different components which components are well known per se, but that in combination displayed a synergy in the inhibition of the progression of prostate cancer as demonstrated by the rising PSA (prostate specific antigen and biomarker for prostate cancer) levels in the blood serum as marker herefore. In this study participants were supplemented over their normal diet with compositions according to the invention or with a placebo and a randomised double blind cross-over study was performed. The group of participants included men with rising prostate specific antigen (PSA) after prostatectomy, radiotherapy or pelvic node dissection. The difference of the increase in the PSA level between active and placebo periods was measured and the

statistical significance was considered. It was found that for the compositions according to the invention the rise in PSA levels was statistically lower compared with the placebo.

Therefore our invention concerns in the first instance a novel composition with anti-prostate cancer activity comprising isoflavonoids, selenium compounds and lycopene(s) and optionally one or more of the following ingredients: a catechin rich source such as green tea extracts, one or more phytosterols, beta-carotene, luteine and tocopherols. It was found that compositions comprising the three imperative components mentioned above already displayed the desired activity. However we also found that other components, mentioned above as optional components could increase this activity. Thus are preferred compositions those wherein at least one of the optional components is present as well.

The isoflavonoids can be present in different forms i.e. they can be present as free isoflavonoids or as glycosilated isoflavonoids or as a mixture of these two. In all instances it was found that the amounts of isoflavonoids in the composition should range from 50 to 99 wt% on total composition. Preferred amounts being 60 to 95 wt% and most preferably from 80 to 90 wt%. All isoflavonoids known can be used, this thus includes natural but also synthetical compounds. However we prefer to apply an isoflavonoid from a natural source. Natural sources are e.g. soy bean and red clover. The isoflavonoids from these sources are in particular relatively rich in genistein

and/or daidzein, formononetin, biochanin and/or glycitein, respectively other red clover components.

The selenium compounds are another essential part of our compositions. These compounds must be present in amounts of 0.01 to 0.2 wt% on total composition. Preferred amounts being 0.03 to 0.1 wt%. Although different types of selenium compounds could be used we prefer to apply selenium compounds that are edible organoselenium compounds, in particular amino acids containing selenium, and more preferably derived from a yeast extract.

The third essential component of our new compositions is a member of the group of lycopene(s). The amount required can range from 0.99 to 49.98 wt% on total composition. Preferred amounts being from 2.5 to 25 wt%. The lycopene(s) could be derived from a natural source, preferably from tomatoes or could be a synthetic product.

As stated above enhanced effects on the inhibition of the progression of prostate cancer were obtained if the compositions also contained other components. In this respect it was found that catechins, in particular catechins as present in green tea extracts are important other components. It is therefore preferred that our compositions also contain catechins of green tea extracts in amounts of 2.5 to 15 times of the weight amount of isoflavonoids.

Alternatively or additionally our compositions can also contain phytosterols. These sterols also contribute to the effects we found for the composition per se. Therefore

we prefer compositions that also contain 2.5 to 25 times of the weight amount of isoflavonoids of one or more phytosterols, preferably phytosterols derived from soy bean or rice bran, and most preferably esterified with fatty acids with 2-24 carbon atoms.

Other beneficial effects were found when beta carotene and/or luteine and/or tocopherols were present in our compositions. Therefore we prefer to add so much beta carotene and/or luteine that in the total composition beta carrotene and/or luteine are present in amounts such that the weight ratios thereof to the amounts of lycopene range from 1:2 to 2:1. Tocopherols are added in amounts such that the weight ratio thereof to the amount of isoflavonoids ranges from 0.1:1 to 5:1.

According to another aspect of our invention we can blend our composition as defined above with other food grade ingredients. This enables an easier dosing and/or addition of the composition of the invention, while also the use of these blends can contribute to the structuring of the food products. Therefore our invention also concerns blends comprising an anti-prostate composition and another component, wherein the anti-prostate composition is the composition according to the invention, while the other component is selected from the group consisting of fats, partial glycerides, emulsifiers, food thickeners, spe's, carbohydrates, proteins, water and fruit juice.

Also the food products containing our novel compositions or blends are part of the invention. Preferred food products are selected from from the group consisting

of fat emulsions, such as spreads, dressings, mayonnaises and creams, bakery products, snacks, ice cream, beverages, cereals and confectionery.

Benefits are also obtained by adding a concentrate of the compositions according to the invention to food products. Therefore our invention also concerns concentrates wherein as active composition the composition according to the invention is present. Preferred concentrates being concentrates, wherein the active composition according to the invention is suspended in a solvent, preferably water or alcohol, while the concentration of the active composition in the concentrate is 10-80 wt%.

The compositions according to the invention can also be applied for the preparation of tablets. This is in particular useful in those instances wherein the active components from our compositions display an off taste. Thus our invention also concerns tablets, wherein the composition according to the invention is present, however supported by a solid carrier, preferably selected from the group consisting of lactose and starch or modified starch.

According to another embodiment of our invention the compositions of the invention can also be applied for the preparation of food supplements. Food supplements are used in addition to the normal meal. A very convenient form for a food supplement is a form wherein the composition according to the invention is encapsulated in an encapsulating material. Materials that can be applied

herefore are the standard encapsulating materials, such as gelatin, sugars or flour or mixtures hereof.

The way the active ingredients of our compositions can be administered to the consumer can differ extensively. In principle every method that leads to the consumption of a required daily dosis can be used for the administering. However we found that the best results are obtained if some of the components are administered via extracts, in particular via green tea extracts, whereas other components are administred via beverages or fat emulsions, e.g. the isoflavonoids and green tea extracts can be administered easily as a beverage, whereas the other components are easier to administer as a fat emulsion.
The required daily doses of the different components are illustrated by the examples.

Further it was found that it is better to administer some components only once a day, while other components better can be administered more than once a day. Therefore we found that a very convenient method for administering to a living being the different active components of a composition with anti-prostate cancer activity, such as compositions according to the invention, is a method wherein the active components isoflavonoids and/or green tea extracts are administered more than once a day, while the other active components are administered only once a day.

Experimental part

Materials and methods:

37 currently untreated prostate cancer patients (N = 37), with rising PSA (selected by means of retrospective visual inspection of the PSA trend) who did not receive hormonal treatment in the past were studied. All patients received a dietary supplement containing putative anti prostate cancer agents (from hereon referred to as verum) or a placebo (which did not contain the putative agents) in a double blind cross over study. It was requested to all participants not to change their regular diet in any way (apart from taking the supplements). During the study the supplements were denoted by the codes Orange and Blue (which of the substances Orange or Blue was verum was unknown during the study). Blood samples were taken weekly. The total study duration was 21 weeks. The first two blood samples were clean and served as reference (baseline) samples (week 1, 2). The day after the 2 nd blood sample was taken half of the patients started with substance Orange, the other half with substance Blue (week 3-8). Both supplements were used for 6 weeks followed by two weeks in which no supplement was used (week 9-10). Following this wash-out period those men who initially took the Blue supplement changed to the Orange one and vice versa (again for six weeks, 11-16). The final phase of the study consisted of a wash-out period of 5 weeks (week 17-21).

Biochemical measurements :

PSA and Free PSA were determined weekly.

Testosterone, LH and SHBG (sex hormone binding globulin) were determined every odd week.

Vitamin E, beta carotene, lycopene and luteine were determined in weeks 3, 8, 11 and 16.

Composition of the supplement (verum) and placebo

The subjects received 20 g/day of a fortified or placebo margarine and 3 fortified or placebo tea-based beverages per day. The full fat margarine contained 70% of fat, w/w and was high in polyunsaturated fatty acids (Unilever Research Vlaardingen, The Netherlands). The verum margarine was supplemented with 0.2 mg selenium (as selenomethionine), 50 α-tocopherol equivalents (α-TE) added as α-tocopherol acetate and 1.5 g phytosterols from soy bean oil esterified with fatty acids. The placebo margarine was free of Selenium and phytosterols and contained small amounts of natural d-α-tocopherol. The beverage, which was consumed 3 times per day, was delivered to the patients as a powder and dissolved in 200 ml of cold tap water. One consumption (200 ml) contained 1 g green tea extract (equivalent to 375 mg of catechins), 40 mg of isoflavonoids (ADM), 3.33 mg of cold-water-soluble β-carotene (Roche Switzerland), 3.33 mg of lutein (3% beadlets CWS, Kemin Foods, USA) and 3.33 mg of water-soluble lycopene (kindly provided by Roche, Switzerland). The placebo beverages contained caffeine similar to the verum product and no isoflavonoids or carotenoids. Placebo and verum beverages were prepared by Lipton (Englewood Cliffs, NJ). The daily amount of verum margarine and verum beverage provided 0.2 mg selenium, 10 mg lycopene, 120 mg isoflavonoids, 3 g green tea extract, 1.5 g phytosterols, 50 mg α-tocopherol, 10 mg lutein and 10 mg β-carotene.

Data analyses performed.

Simple statistical analysis of PSA data.
The slopes of 2 log PSA as a function of time were assessed (linear fit) and compared for the Blue and Orange period by means of Wilcoxon's matched pairs tests for those men who had complete Orange and Blue episodes (complete case analysis).

Advanced statistical analysis of PSA data.
As the simple analysis underestimates the noise present in the signal (too much of the noise is assessed as effect) and, more importantly, as the method does not take into account all measured information (wash out periods, run in period) a different approach was taken using a broken stick model. Two variants of this model featured in this study. The first model assumes a linear relationship between 2 log PSA and time and allows for a different slope during the orange phase of the study (denoted as the Orange model). The second model allows for a different slope during the Blue period (denoted as Blue model). This model includes the multilevel structure of the data using the concept of plates. Multilevel data here means that our data consists of 37 seven men (the highest level in the data hierarchy) in whom (ideally) 21 PSA samples are taken (the second highest level in the data hierarchy).

The following fitting strategy was applied.
First the blue model was fitted to all data measured until the start of orange period (denoted by "no orange, blue model"). In this way the orange period and all data

measured after that were left out to assure that the orange substance did not affect the fit of the Blue model. In the same way, to study the effect of the Orange substance, the orange model was fitted to all data measured until the start of the Blue period ("no blue, orange model"). On the basis of the outcomes of these fits (see Results section) the Orange model was fitted to all data ("all data orange model"). All fits were done with the freely available software package BUGS using a Monte Carlo Markov Chain simulation approach. Vague (i.e. non informative) priors were used for the "to be fitted distributions" (O/B, alpha, blue, sigma). For all fits the mean and variance of the underlying distributions were estimated.

The presence of a period effect was studied by comparing the orange slope deviations where Blue was given after orange by those where Blue was given first.

Analysis of hormone data.

LH data. An average called LHref was calculated as the average of LH in weeks 1, 19 and 21. LHOrange was calculated as the 3 week average LH value during the Orange period. LHBlue was defined as the three week average LH value during the Blue period.

Identical variables were defined for testosterone, SHBG and the free androgen index FAI defined as testosterone / SHBG.

Analysis of the anti oxidants: Vit E, lycopene, luteine beta carotene, contents were determined in plasma by reserve phase HPLC.

The average levels of Vit E, lycopene luteine and beta carotene were determined during the study periods Orange

and Blue. Comparison was done by means of Wilxocon's matched pairs test.

Correlation between hormone data and PSA response. Changes in the PSA slope were compared to changes in the levels of testosterone and the free androgen index by means of the linear correlation coefficient.

Results

After the trial had finished the code was broken. The Orange substance contained the putatively effective agents, the blue substance was the placebo.

Statistical analyses.

Complete case analysis of the slopes during the Orange and Blue period (N = 19).
During the Orange period the average slope of the 2log PSA as function of time was 0.0168 corresponding to a doubling time of 60 weeks, during the Blue period it was 0.0339 corresponding to a doubling time of 29.5 weeks (p = 0.10, 2-sided, Wilcoxon's matched pairs test).

Bugs analyses using the Blue and Orange model (N=37).
The results of the "No orange data, blue model", "No blue, orange model" and "All data, orange model" fits are given in Table 1. It is clear that the blue substance has no decreasing effect to the "normal" PSA slope (O/B parameter mean = -0.044, sderr = 0.01, the negative sign corresponds to an increase of the PSA slope). The "no blue, orange model" results however show a promising result for the orange substance. The results of the "all data, orange model" fit (O/B) make it very likely that the orange substance indeed reduces the PSA slope by some 26% (equivalent to a 26% increase of the doubling time).

Hormone data
The results of the measurements of hormones during the study and the comparison of the average for different

periods (reference, orange and blue) are given in Table 2. No significant differences are observed between the periods for SHBG and LH. Testosterone is significantly lower in the orange period when compared to the reference period. Remarkably testosterone is also lower during the Blue period and it is therefore not surprising that, though testosterone is on average lower in the orange period when compared to the blue period, commonly used thresholds to denote significance are not met. For the free androgen index this remarkable pattern is observed again (even stronger, p value of the comparison of FAI during the blue and orange period is 0.24). A long lasting hormonal effect of the orange substance which would effect the hormone levels measured during the blue period where blue is given later than orange was ruled out by limiting the analysis to those cases were orange was given after blue.

Anti oxidant data.

The average levels of lycopene, beta carotene, luteine and vitamin E for the two study periods are given in Table 3. All compounds studied were significantly increased during the Orange period indicating that the Orange substance was quite effective in increasing the serum/plasma levels of the putative agents.

Though the formally used two sided p-value thresholds are not met, the results of our study strongly suggest an effect of the putative effective agents on PSA progression.

Parameter	No blue, orange model	No orange, blue model	All data, orange model
Mean deviation from slope during orange (standard error, pvalue)	0.48 (0.02, p < 0.001)		0.26 (0.15, p < 0.09)
Mean deviation from slope during blue (standard error, pvalue)		-0.044 (0.01, p < 0.001)	
Mean slope (standard error, pvalue)	0.02 (0.0049, p < 0.001)	0.03 (0.0046, p < 0.001)	0.024 (0.0032, p < 0.001)
Mean intercept (standard error, pvalue)			1.66 (0.43, p < 0.001)

Table 1

	Period, number of valid samples					
	Orange	Reference	Blue	Reference	Orange	Blue
Hormonal Data	Mean,N	Mean,N, P value Orange-Ref	Mean,N	Mean,N, p value Blue-Ref	Mean,N	Mean,N p value Orange-Blue
Testos-terone	15.0 (N=31)	17.5 (N=27) p < 0.001	15.7	17.5 p = 0.01	15.0	17.5 p = 0.07
FAI	0.2 (N=31)	0.23 (N=27) p < 0.001	0.20	0.23 p = 0.28	0.20	0.20 p = 0.24
LH	0.74 (N=31)	0.69 (N=28) p = 0.19	0.73 (N=32)	0.69 (N=28) p = 0.69	0.74 (N=31)	0.73 (N=32) p = 0.38
SHBG	4.3 (N=31)	4.3 (N=28) p=0.77	4.3 (N=32)	4.3 (N=28) p = 0.77	4.3 (N=31)	4.3 (n=32) P = 0.39

Table 2

Hormone data. Comparison between hormone levels during thedifferent study periods (Wilcoxons matched pairs data).

Anti oxidants	Anti oxidants Orange	Anti oxidants Blue, p-value
Carotene	1368.7	615.6, < 0.001
Lycopene	650.3	314.3, < 0.001
Luteine	260.0	123.2, < 0.001
Vitamine E	33.2	29.0, < 0.001

Table 3

Anti oxidant data. Comparison between study periods (Wilcoxons matched pairs test).

Claims

1. Composition with anti-prostate cancer activity comprising isoflavonoids, selenium compounds and lycopene(s) and optionally one or more of the following ingredients: a catechin rich source such as green tea extracts, one or more phytosterols, beta-carotene, luteine and tocopherols.

2. Composition according to claim 1, wherein the isoflavonoids are present as free isoflavonoids or as glycosilated isoflavonoids or as a mixture hereof in amounts of 50-99 wt% on total composition.

3. Composition according to claims 1-2, wherein the selenium compounds are present in amounts of 0.01 - 0.2 wt% on total composition.

4. Composition according to claims 1-3, wherein the lycopene(s) are present in amounts of 0.99 - 49.98 wt% on total composition.

5. Composition according to claims 1-2, wherein the isoflavonoids are derived from soy bean or red clover and are relatively rich in genistein and/or daidzein and/or glycitein, and/or biochanin and/or formononetin.

6. Composition according to claims 1 and 3, wherein the selenium compound is an edible organoselenium compound, in particular an amino acid containing selenium, preferably derived from a yeast extract.

7. Composition according to claims 1 and 4, wherein the lycopenes are derived from tomatoes, or a synthetic product.

8. Composition according to claims 1-7 wherein the composition also contains catechins of green tea extracts in amounts of 2.5 to 15 times of the weight amount of isoflavonoids.

9. Composition according to claims 1-8 wherein the composition also contains 2.5 to 25 times of the weight amount of isoflavonoids of one or more phytosterols, preferably phytosterols derived from soy bean or rice bran, and most preferably esterified with fatty acids with 2-24 carbon atoms.

10. Composition according to claims 1-9 wherein the composition also contains beta carotene in a weight ratio to lycopene of 1:2 to 2:1.

11. Composition according to claims 1-10, wherein the composition also contains luteine in a weight ratio to lycopene of 1:2 to 2:1.

12. Composition according to claims 1-11 wherein the composition also contains tocopherols in a weight ratio to the isoflavonoids of 5:1 to 0.1 to 1.

13. Blends comprising an anti-prostate composition and another component, wherein the anti-prostate composition is the composition according to claims 1-12, while the other component is selected from the group consisting of fats,

partial glycerides, emulsifiers, food thickeners, spe's, carbohydrates, proteins, water and fruit juice.

14. Food products containing a health component, wherein the health component is a composition according to claims 1-13.

15. Food compositions according to claim 14 wherein the food composition is selected from the group consisting of fat emulsions, such as spreads, dressings, mayonnaises and creams, bakery products, snacks, ice cream, beverages, cereals and confectionery.

16. Food supplements with anti-prostate cancer activity, wherein the supplements contain as active component the composition according to claims 1-13, preferably in encapsulated form.

17. Concentrates and tablets with anti-prostate cancer activity, wherein the tablets or concentrates contain as active component the composition according to claims 1-13.

18. Concentrates according to claim 17, wherein the active composition according to claims 1-13 is suspended in a solvent, preferably water or alcohol, while the concentration of the active composition in the concentrate is 10-80 wt%.

19. Tablets according to claim 17, wherein the active composition according to claims 1-13 is supported by a solid carrier, preferably selected from the group consisting of lactose, starch and modified starch.

20. Method for administering the active components of a composition with anti-prostate cancer activity according to claim 8 to a living being wherein the active components isoflavonoids and/or green tea extracts are administered more than once a day, while the other active components are administered only once a day.

21. Method according to claim 20, wherein the isoflavonoids and/or green tea extract is administered as a beverage, whereas the other active components are administered as a fat emulsion.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 00/09933

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78 A61K31/198 A61K31/01 A23L1/30 A61P35/00
A61K31/352 A61K31/35 //(A61K35/78,31:195,31:01),(A61K31/35,
31:195,31:01),(A61K35/78,35:78,31:195,31:01),(A61K35/78,31:35,

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 7 A61K A23L

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 33494 A (KOSBAB JOHN V) 6 August 1998 (1998-08-06) *Formula IK on pages 4 to 6; Formula IVF on pages 13 to 15 * page 20, line 9 -page 20, line 10 page 24, line 3 -page 24, line 30 page 26, line 27 -page 26, line 33 ---	1-21
X	G J KELLOF ET AL: "Chemoprevention of prostate cancer: concepts and strategies" EUROPEAN UROLOGY, vol. 35, no. 5-6, 1999, pages 342-350, XP000872008 tables 3,4 * "promising agents for prostate cancer chemoprevention" on page 346 * --- -/--	1-21

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 January 2001	18/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pilling, S

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 00/09933

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 31:195,31:01)

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)

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	R CHILLOT: "Guard against your secret fear" PREVENTION, vol. 51, no. 7, July 1999 (1999-07), pages 120-127, XP000872194 page 123, column 1 -page 124, column 2 ---	1-21
X	DATABASE HEALTH & WELLNESS (ONLINE) File 149 DIALOG (THE GALE GROUP) Full Text Accession No. 01793015, Oct 1998 (1998-10) "The perfect meal (meals with health benefits)(includes recipes)" XP002129571 the whole document --- -/--	1-21

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Date of the actual completion of the international search	Date of mailing of the international search report
3 January 2001	

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) 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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INTERNATIONAL SEARCH REPORT

Information on patent family members

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