(71) Applicant (for all designated States except US): GIULIANI S.P.A. [IT/IT]; Via P. Palagi, 2, I-20129 Milano (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): NACCARI, Giancarlo [IT/IT]; Via Bellinzona, 7, I-20052 Monza (IT). BARONI, Sergio [IT/IT]; Via Piazzolo, 3, I-24030 Villa d'Adda (IT). TRIMBOLI, Domenico [IT/IT]; Via Ostiense, 60/D, I-00154 Roma (IT).

(74) Agent: APPOLONI, Romano; Notarbartolo & Gervasi S.p.A., Corso di Porta Vittoria, 9, I-20122 Milan (IT).

(54) Title: COMPOSITION WITH ANTIOXIDANT ACTIVITY FOR PHARMACEUTICAL OR DIETARY OR COSMETIC USE.

(57) Abstract: The invention provides a composition with antioxidant activity for pharmaceutical or dietary or cosmetic use, characterised by comprising as active principle a combination of resveratrol, catechin and caffeic acid. In particular, pharmaceutical use of the composition is aimed at the treatment and prevention of all disorders consequent on oxidatives stress, in particular chronic inflammatory pathologies.
COMPOSITION WITH ANTIOXIDANT ACTIVITY FOR PHARMACEUTICAL OR DIETARY OR COSMETIC USE

DESCRIPTION

The present invention relates to a composition with antioxidant activity for pharmaceutical or dietary or cosmetic use.

It is noted that a moderate consumption of red wine is associated with a reduction in the incidence of cardiovascular events (More, Medicine 1986:65:245-67; Graziano, N Engl J Med 1993:329:1829-34). Components of red wine such as flavonoids are thought to be beneficial to the cardiovascular system by virtue of their capacity to inhibit platelet function.

The same Applicant is author of the patent EP1328268 in which a composition with antioxidant activity for pharmaceutical or dietary or cosmetic use is described, characterised by comprising as active principle a combination of the flavonoids catechin and quercetin, which exhibit synergistic activity, when associated in reciprocal molar ratios selected within a critical range, extending from 6:1 to 3:1 moles of catechin:quercetin.

It is noted that said oxidative stress favours numerous pathologies. It is also noted that there are various pathological conditions in the pathogenesis of which oxidative stress appears to play an important role. Oxidative events are particularly notable in various conditions such as: hypoxia, inflammation, irradiation by ultraviolet light, alcohol abuse, ageing.

The following is a list of some of the principal pathologies in which oxidative stress is implicated: atherosclerosis, ischemic cardiopathy, cerebral vascular insufficiency, complications of diabetes, hypertension, nephropathy, retinopathy, cataracts, chronic hepatopathies, neurodegenerative pathologies (Alzheimer, Parkinson), tumours, immunodeficiencies, chronic colitises.

The present invention proposes as its object the prevention and treatment of oxidative stress in general and of all consequent pathologies, in particular chronic inflammatory pathologies and cardiovascular diseases.

Within this framework of the art it has been surprisingly found, and constitutes an aspect of the present invention, that a selected combination of the three flavonoids resveratrol, catechin and caffeic acid is able to develop antioxidant activity with
synergistic action.

In particular, the invention provides a composition with antioxidant activity for pharmaceutical or dietary or cosmetic use, characterised by comprising as active principle a combination of resveratrol, catechin and caffeic acid.

In such composition the molar ratio of caffeic acid to catechin is preferably within the range from about 1:2 to 1:6, respectively.

Even more preferably, the molar ratio of caffeic acid to catechin is about 1:4, respectively.

Moreover, the molar ratio of resveratrol to caffeic acid in the composition of the invention is preferably within the range from about 1:3 to 1:9, respectively.

Even more preferably the molar ratio of resveratrol to caffeic acid is about 1:6, respectively.

The invention here described has its origin in experimental observations gained by a study, hereinafter reported as an example to better describe the action of said active principle and in no way limiting the scope of the invention, conducted with the initial aim of investigating if a moderate daily consumption of wine influences oxidative stress and platelet function.

STUDY

Study plan

20 healthy volunteers not presenting signs of cardiovascular diseases and without risk factors for atherosclerosis such as hypertension, diabetes, dyslipidemia, obesity, or a smoking habit, were examined.

None of the subjects had taken antioxidant vitamins or other types of antioxidant or antiplatelet medication in the month prior to the study.

All the subjects were subjected to a period of preparation of one week during which they abstained from drinking wine or alcoholic drinks and NSAID and were subjected to a verification of the type of diet they normally followed.

All followed a typical Mediterranean diet based on carbohydrates, olive oil, fruit and vegetables with no evident differences in the quantity of flavonoids consumed with food. After the preparation phase, the subjects were randomly assigned to consume either 300 ml/day in total of red wine (n=10, males 4, females 6, average age 45 ± 6) or white wine (n=10, males 5, females 5, average age 42 ± 5) during
lunch. During the entire observation period, any other type of alcoholic beverage was prohibited. At baseline conditions and after 15 days of observation, a blood sample was taken between 8.00 and 9.00 am from every subject who had fasted for at least 12 hours; therefore the interval between the last intake of wine and the blood sampling was 12 hours. A bottle of wine (750 ml) was delivered to each subject every two days and the amount remaining in each bottle was measured to verify compliance. One of the subjects randomly assigned to the white wine group followed the protocol for two weeks but then refused to return for testing for blood changes. In addition to the routine analyses, the laboratory study consisted of measuring the latent period of collagen-induced platelet aggregation, collagen-induced H$_2$O$_2$ formation and plasma flavonoid concentration.

**Preparation of the platelets**

Blood mixed with 0.13 mM of sodium citrate (9:1 ratio) was collected from each subject.

For the flow cytometric analysis and for the in-vitro study of the effect of flavonoids on platelet aggregation, the platelets were separated from plasma proteins by centrifugation and suspended in calcium-free Tyrode's buffer containing 0.2% bovine serum albumin, 5 mMol/L glucose and 10mmol/L Hepes, pH 7.35; the cell suspension was adjusted to give a final concentration of 2 x 10$^8$ cells/ml.

**Flow cytometric analysis**

The platelet suspension (2 x 10$^8$ cells/ml) was incubated (15 minutes at 37°C) with DCFH-DA (40 µmol/L) and activated with 2 µg/ml of collagen. The reaction was interrupted after one minute with EGTA 2mmol/L.

All the samples were analysed using a Coulter XL-MCL flow cytometer (Hialeah, USA) equipped with an argon laser (480 nm emission). The instrument was calibrated for measuring logarithmic forward light scatter (LFS) which is a measure of particle size, logarithmic 90° light scatter (LSS) which is a measure of cell granularity, and green fluorescence (DCF) at 510-550 nm (LFL1). The fluorescent signal generated by the sample was expressed in the in-vitro study as Index of Stimulation (I.S. = intensity of mean channel fluorescence of stimulated platelets/ intensity of mean channel fluorescence of non-stimulated platelets. In the ex-vivo study, the fluorescence parameters were expressed as arbitrary units (a.u.)
Aggregation test
The latent period of collagen-induced platelet aggregation was evaluated by measuring the time delay between adding the agonist and the start of platelet aggregation. The determination was calculated with a specific aggregometer (Helena Laboratories: Beaumont, Texas). The platelets in the in-vitro study (2 x 10^8 cells/ml) were pre-incubated in either the presence of catechin (0.2 μM), caffeic acid (0.2 μM) and resveratrol (0.5 μM), used either individually or together (30 minutes at 37°C for each incubation) before activation with collagen (2 μg/ml), or in their absence.

Measurement of plasma flavonoids
Chemical substances
Resveratrol, (+)-catechin, caffeic acid, quercetin and β-glucoronidase (EC 3.2.1.31) from Helix Pomatia, type H-2, were acquired from Sigma (St. Louis, MO, USA). β-glucoronidase activity was 105,000 units/ml and sulphatase activity was 343,000 units/ml. Methanol and ethyl acetate were of HPLC grade and were acquired from Carlo Erba (Milan, Italy).

Enzymatic treatment of plasma
The plasma samples were incubated with a hydrolysing solution to obtain free phenolic compounds. Briefly: 1.5 ml of plasma were mixed with 2 ml 100 mM acetate butter (pH 5.0) containing 4,000 units of glucuronidase plus 200 units of sulfatase. The mixture was incubated for 1 hour at 37°C and then extracted three times with ethyl acetate; 3.0 ml of ethyl acetate were added each time and the mixture was agitated for 4 minutes. After having centrifuged the mixture for 5 minutes at 3,500 r.p.m., the upper layers were removed. The combined extracts were made to pass through anhydrous sodium sulphate and dried under nitrogen. The samples were conserved at -70°C until required.

Configuration and HPLC analysis
The separation of free phenolic compounds was achieved as previously described. Briefly: the HPLC system was formed from a Perkin Elmer series 410 Lc pump with a SEC-4 control element for the gradient elution. The mobile phase was formed from two solutions: solution A was 0.22 M acetic acid, solution B was methanol. A binary gradient (between 7 and 24%) was applied, at a flow rate of 1
ml/min, to a Wakosil II 5C18 RS analytical column (5 μm, 150 x 4.6 mm internal diameter, SGE) equipped with a 10 mm SGE pre-column and maintained at 30°C. The plasma extracts were re-dissolved just before the analysis in methanol and 20μL were injected into the system. The eluate was monitored with a Coulochem II electrochemical detector (ESA, Bedford, MA, USA) equipped with a model 5011 analytical cell. The settings were the following: the first electrode was set at −100 mV and the second electrode (the analytical electrode) at +600 mV. The detector output was recorded on a Perkin Elmer Turbochrom Chromatography workstation. The detection limit of the procedure was < 0.2 ngr/ml.

Identification of ethanol

For plasma ethanol levels, a colorimetric kit was used (SIGMA Diagnostic, procedure 333-UV based on the production of NADH after alcohol oxidation by alcohol dehydrogenase).

Statistical analysis

Statistical analysis was undertaken by the chi square statistical test and appropriate t-test. Where necessary the data were normalized using logarithmic transformation. The effect of the treatment was analysed by analysis of variance (ANOVA) of two-way repeated measurements. The data were presented as mean ± SD, median and 95% tolerance limits. To evaluate the statistical significance only “two-tail” probabilities were used. A value p < 0.05 was considered as statistically significant (16). All calculations were executed using personal computer software (Stat View II, Abacus Concepts, Berkeley, California).

Results

Ex-vivo study

At baseline conditions no difference in the latent period of collagen-induced platelet aggregation was observed between the two groups. At the end of the treatment the latent period was prolonged by 57.5% (p < 0.002) in subjects who had consumed white wine and by 148.0% (p < 0.001) in subjects treated with red wine. The two groups presented a significant difference in the latent period at the end of treatment (p < 0.05).

At baseline conditions the formation of platelet H₂O₂ not stimulated and induced by the collagen was similar in both groups. At the end of the treatment, formation of
H₂O₂ not stimulated and induced by the collagen was reduced by 22.0% (p < 0.03) and by 24% (p < 0.03) respectively in the subjects who had consumed white wine, and by 55.0% (p < 0.02) and by 54.5% (p < 0.02) respectively in the subjects who had consumed red wine. At the end of the treatment it was observed that platelet H₂O₂ formation was significantly lower in subjects treated with red wine compared with those who had consumed white wine (p < 0.05).

Four flavonoids were measured in human plasma, namely resveratrol, caffeic acid, catechin and quercetin. The latter was the only one not determinable before and after wine consumption. Catechin was nearly undetectable at the start, but increased after consumption of both red and white wine; caffeic acid increased with red wine and white wine, while resveratrol increased only after consumption of red wine. The results are reported in the following table 1.

**TABLE 1**
Plasma flavonoid content (mean ± SEM) expressed in ng/ml before and after consumption of wine (*p < 0.02 Anova post hoc test; $p < 0.007$ between the two groups after 15 days' wine consumption).
ND = not determinable

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<th>FLAVONOIDS (ng/ml)</th>
<th>WHITE WINE</th>
<th>RED WINE</th>
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<td>BEFORE</td>
<td>AFTER</td>
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<tr>
<td>Catechin</td>
<td>ND</td>
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<tr>
<td>Caffeic Acid</td>
<td>13.5±21.0</td>
<td>30.7±21.1</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>161±85.2</td>
<td>157.1±150.4</td>
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</tbody>
</table>
| Total flavonoid content | 157.1±70.0 | 170.4±66.2 | 185.7±44.7 | 453.0±48.4$*$$

Increases in individual flavonoids observed after red or white wine consumption were not significant. The sum total of the three flavonoids in plasma were similar
at baseline conditions; after consumption of white wine, the plasma flavonoids increased but not significantly (+8%, \( p > 0.05 \)), while after consuming red wine the increase was statistically significant (+143%, \( p < 0.007 \)). At the end of the treatment plasma flavonoids were significantly higher in subjects who had consumed red wine than those in the white wine group (\( p < 0.007 \), table 1).

Plasma ethanol was not detectable either before or after red or white wine consumption.

On the basis of the preceding observations, the following study was carried out on a selection of the three flavonoids resveratrol, caffeic acid and catechin.

**In vitro study**

The attached figures 1 and 2 show, respectively, the latent period of platelet aggregation and formation of collagen-induced platelet \( \text{H}_2\text{O}_2 \) (administered at a concentration of 2 \( \mu \text{g/ml} \)), for the three flavonoids resveratrol, caffeic acid and catechin, both individually and in combination (mix), at the concentrations specified therein: catechin (0.2 \( \mu \text{M} \)), caffeic acid (0.2 \( \mu \text{M} \)) and resveratrol (0.5 \( \mu \text{M} \)), in both cases referred to a control.

In fig. 1 it can be observed that the latent period of collagen-induced platelet aggregation (lag phase (sec)) was not influenced by caffeic acid, catechin or resveratrol individually; however the simultaneous incubation of platelets with the three flavonoids in combination (mix) significantly prolonged the latent period by 130.0% (\( p < 0.01 \)). As can be observed in fig. 2, the formation of collagen-induced platelet \( \text{H}_2\text{O}_2 \) (SI) was only slightly influenced by caffeic acid or resveratrol, and negligibly by catechin: however simultaneous incubation of platelets with the three flavonoids in combination (mix) induced significant inhibition of \( \text{H}_2\text{O}_2 \) (-51%, \( p < 0.01 \)).

From the aforesaid observations, a synergistic antioxidant action by the three selected flavonoids in combination can therefore be deduced.

Said selective combination of the present invention is indicated for use as active principle for: atherosclerosis, ischemic cardiopathy, cerebral vascular insufficiency, complications of diabetes, hypertension, nephropathy, retinopathy, cataracts, chronic hepatopathies, neurodegenerative pathologies (Alzheimer, Parkinson) tumours, immunodeficiencies, chronic colitises.
The active principle proposed by the present invention can be conveniently formulated in compositions in which catechin is preferably present in a quantity between 1.5 and 30.0 mg/dose, caffeic acid from 1.25 to 5.0 mg/dose and resveratrol from 0.25 to 9.0 mg/dose.

Tablets, capsules, granules and the like are preferred pharmaceutical or dietary forms for oral use. Non-limitative examples of practical implementations of pharmaceutical or dietary compositions (supplements) for oral use according to the present invention are hereinafter described.

**EXAMPLE 1**

**Capsules**

- Catechin: 7.50 mg
- Caffeic acid: 1.25 mg
- Resveratrol: 0.25 mg
- Microcrystalline cellulose: 88.20 mg

**EXAMPLE 2**

**Tablets**

- Catechin: 15.0 mg
- Caffeic acid: 2.5 mg
- Resveratrol: 0.5 mg
- Calcium phosphate dibasic dihydrate: 67.0 mg
- Microcrystalline cellulose: 60.0 mg

**EXAMPLE 3**

**Chewable tablets**

- Resveratrol: 9.0 mg
- Caffeic acid: 5.0 mg
- Catechin: 1.5 mg
Mannitol 315.3 mg
Sorbitol 33.3 mg
Crosivodone 16.0 mg
Flavours 15.0 mg
Magnesium stearate 4.0 mg
Aspartame 0.6 mg
Acesulfame K 0.3 mg

EXAMPLE 4
Sachets
Catechin 30.0 mg
Caffeic acid 5.0 mg
Resveratrol 1.0 mg
Sorbitol 1872.5 mg
Flavours 40.0 mg
Citric acid 29.0 mg
Maltodextrin 15.0 mg
Aspartame 6.0 mg
Acesulfame K 1.5 mg

EXAMPLE 5
Drinkable vials
Catechin 30 mg
Caffeic acid 5 mg
Resveratrol 1 mg
Gynostemma Pentaphyllum 10 mg
Huperzia serrata 5 mg
Fructose 2 g
Grapefruit seed extract 3 mg
Water remainder to 10 ml

EXAMPLE 6
Sustained release tablets (Retard)
Catechin 30 mg
Caffeic acid 5 mg
Resveratrol 1 mg
Methyl sulphonyl methane 200 mg
Vitamin C 60 mg
Vitamin E 15 mg
Vitamin B6 3 mg
Calcium pantothenate 4.5 mg
d-biotin 0.225 mg
Zinc (as AA chelate) 7.50 mg
Copper (as AA chelate) 1.25 mg
Manganese (as AA chelate) 2.25 mg
Microcrystalline cellulose 102 mg
Calcium phosphate dibasic dihydrate 83 mg
Hydroxypropylmethylcellulose 50 mg
Magnesium stearate 8 mg
Silicon dioxide 2.5 mg

EXAMPLE 7
Cosmetic topical lotion
Catechin 30 mg
Caffeic acid 5 mg
Resveratrol 1 mg
Hydrolysed soya proteins 15 mg
Calcium pantothenate 15 mg
Biotin 0.15 mg
Grapefruit seed extract 30 mg
EDTA 3 mg
Hydrogenated castor oil 30 mg
Fragrance 6 mg
Cosmetic alcohol 750 mg
Water remainder to .5 mL

EXAMPLE 8
Cosmetic topical cream
Catechin 300 mg
Caffeic acid 50 mg
Resveratrol 10 mg
Cetylstearyl alcohol 3.8 g
Crodamol (quaternium-9 cetrimonium methosulfate cetearyl alcohol) 2.5 g
Emulium 22 (tribehenin PEG-20 esters octyldodecyl myristate) 2 g
Monoi butter 0.5 g
Cannabis sativa oil 0.25 g
Jaguar excel 0.1 g
Hydrolyzed soya protein 0.2 g
Cyclomethicone 3 g
Calcium pantothenate 30 mg
Biotin 3 mg
Ultrasil A23 1 g
Fragrance 0.5 g
Water 85 g
CLAIMS

1. Composition with antioxidant activity for pharmaceutical or dietary or cosmetic use, characterised by comprising as active principle a combination of resveratrol, catechin and caffeic acid.

2. Composition as claimed in claim 1 characterised in that the molar ratio of caffeic acid to catechin is within the range from about 1:2 to 1:6, respectively.

3. Composition as claimed in claim 2 characterised in that the molar ratio of caffeic acid to catechin is about 1:4, respectively.

4. Composition as claimed in claim 1 characterised in that the molar ratio of resveratrol to caffeic acid is within the range from about 1:3 to 1:9, respectively.

5. Composition as claimed in claim 4 characterised in that the molar ratio of resveratrol to caffeic acid is about 1:6, respectively.

6. Composition as claimed in claim 1 characterised in that the catechin is present in a quantity from 1.5 to 30.0 mg/dose, the caffeic acid from 1.25 to 5.0 mg/dose and the resveratrol from 0.25 to 9.0 mg/dose.

7. Composition as claimed in claim 1 characterised by being indicated for use in the treatment or in the prevention of disorders resulting from oxidative stress, chronic inflammatory pathologies and cardiovascular diseases.

8. Composition as claimed in claim 1 characterised by being indicated for use in the treatment or the prevention of at least one of the following pathologies: atherosclerosis, ischemic cardiopathy, cerebral vascular insufficiency, complications of diabetes, hypertension, nephropathy, retinopathy, cataracts, chronic hepatopathies, neurodegenerative pathologies (Alzheimer, Parkinson) tumours, immunodeficiencies, chronic colitises.

9. Composition as claimed in claim 1 characterised by being formulated for oral use.

10. Composition as claimed in claim 1 characterised by being formulated for topical use.

11. Use of a combination of resveratrol, catechin and caffeic acid as active principle in the preparation of a composition with antioxidant activity for pharmaceutical or dietary or cosmetic use.

12. Use as claimed in claim 11 wherein the molar ratio of caffeic acid to catechin is
within the range from about 1:2 to 1:6, respectively.

13. Use as claimed in claim 11 wherein the molar ratio of resveratrol to caffeic acid is within the range from about 1:3 to 1:9, respectively.
FIG. 1
INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/007506

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23L/03 A23L/30 A61K7/00 A61K31/353

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 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)
EPO-Internal, WPI Data, PAJ, FSTA, BIOSIS, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.

X US 6 238 673 B1 (HOWARD ALAN NORMAN) 29 May 2001 (2001-05-29) column 2, line 9 - column 3, line 18; table 1 column 7, lines 63-65 column 9, paragraph 4 1,6-13

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:
*A* document defining the general state of the art which is not considered to be of particular relevance
*E* earlier document but published on or after the international filing date
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
*C* 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

Date of the actual completion of the international search 22 October 2004

Date of mailing of the international search report 05/11/2004

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 Hl Ptovert Tel. (+31-70) 340-2010, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer

Koch, J
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<td>FRANKEL E N ET AL: &quot;PRINCIPAL PHENOLIC PHYTOCHEMICALS IN SELECTED CALIFORNIA WINES AND THEIR ANTIOXIDANT ACTIVITY IN INHIBITING OXIDATION OF HUMAN LOW-DENSITY LIPOPROTEINS&quot; JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, no. 4, 1995, pages 890-894, XP000497580 ISSN: 0021-8561 table 2</td>
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From PCT/ISA/E19 [patent family annex] (January 2004)