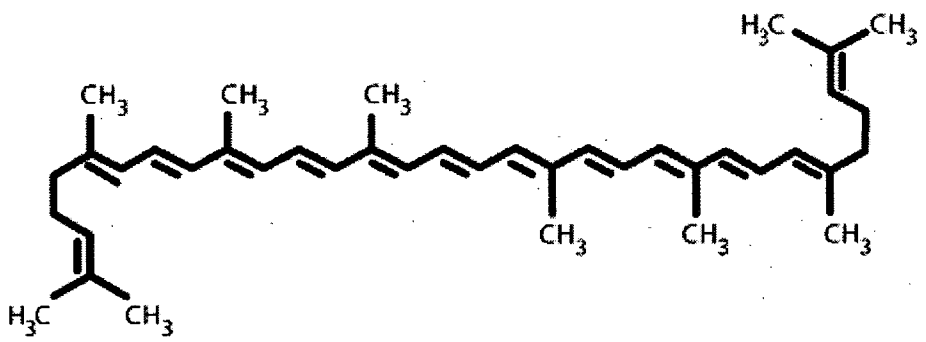
Lycopene and resveratrol dietary supplement

TECHNICAL FIELD

[001] This invention generally relates to dietary supplement. It relates specifically to such dietary supplement compositions comprising lycopene and resveratrol exhibiting certain therapeutic effects, including anti-oxidant, anti-arthritis, suppressing carcinoma growth and mitigating hyperlipoidemia.

BACKGROUND ART

[002] Lycopene, with a molecular formula of $C_{40}H_{56}$ and molecular weight of 536.85, has a molecular structure shown below.



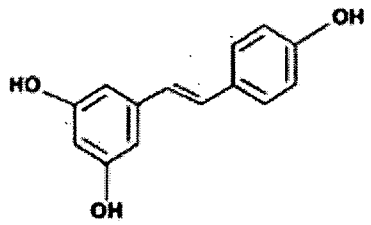
[003] It is a carotenoid and the major target organs and tissues of lycopene in the human body are testis, prostate, liver and intestines. It is found to reduce incidence of prostatic carcinoma, metrocarcinoma, and pancreatic carcinoma more effectively than ß-carotene (Giovannucci E., 1999, Gann P.H., 1999). As early as 1989, lycopene has been found to have the highest activity in quenching oxygen-singlet among all carotenoids including ß-carotene (Di Mascio P.). The anti-oxidative activity of lycopene is found to be about 3.2-fold of that of ß-carotene, and 100 times of that of vitamin E. Applied orally and absorbed through the intestinal tract, lycopene quenches free-radicals and thus protects tissues, cells, and DNA from oxidation by the free-radicals.

[004] Previous studies have revealed a number of functions of lycopene: anti-ageing, enhancing immune health, reducing risk of cardiovascular diseases and incidence of malignancies, especially oral, throat, gastric, colon and uterus carcinomas. A meta-analysis carried out at Harvard University including 47,000 participants over a period of 6 years found that the incidence of prostatic carcinoma was over 30% lower in the lycopene group (Giovannucci, E., 1995). Furthermore, clinical trials revealed activity of lycopene in suppressing tumor growth and metastasis, especially effective for pancreatic, lung and gastric carcinomas (Giovannucci E., 1999; Gann R.H., 1999)

[005] Because of its multiple beneficial effects, lycopene is now recognized

as a star healthy food supplements in the 21st century and is gaining in popularity world-wide. Especially in developed countries including the U.S., Western Europe, Japan and Israel, huge wealth and efforts have been invested in related researches and in development of lycopene-containing drugs, food supplements, foods and cosmetics since 1990.

[006] Resveratrol, with a molecular formula $C_{14}H_{12}O_3$ and a molecular weight of 228.25, is a terpenoid which is mainly contained in grape skin, peanut, pineapple and knotweed rhizome. This compound appears as an insipidity white crystal powder, slightly soluble in water but soluble in organic solvents such as ethanol and acetone. The structural formula of resveratrol is shown below.



$C_{14}H_{12}O_3$ 228.25

[007] Resveratrol is known as an antioxidant, and has been found to decrease blood viscidity, suppress platelet–coagulation, enhance vasodilation and thus promote blood circulation. Because of its hypolipidemic feature, resveratrol plays an important role in preventing atherosclerosis and ischemic heart diseases. Resveratrol also has antineoplastic effect and is a natural substitute of estrogen. Further functionalities of resveratrol include

anti-ageing effect, preventing oxidation of low-density lipoprotein (LDL) cholesterol, anti-inflammation and anti-allergic effect.

[008] The main application of resveratrol is directed to acute infectious hepatitis, menostasis, rheumatism, bone and muscle pain, bronchitis, cholecystolithiasis, hypercholesterol and hypertriglyceride condition. The major target organs and tissues of resveratrol in human body are heart, blood vessels and skins.

[009] There exist a number of patents either one of lycopene and resveratrol as the essential compound with optionally the other compound, or with both compounds in specific range of ratios which are claimed to be therapeutic for various ailments. New Zealand Patent No. 526350 (al-Shakarchi) disclosed lycopene in 0.1 – 2% w/v and resveratrol in 0.05 – 1.5% w/v in a preferred combination of a main complex composition which comprises metal salts, amino acids, amino alcohol and vitamin B complex. The lycopene : resveratrol disclosed is in the range of 1:15 – 40:1.

[010] In U.S. patent publication No. 2008/0262081 (Raederstorff) lycopene with resveratrol is disclosed for anti-aging effect in form of a dietary supplement in wide-ranging ratios from about 1:1430 – 24:1. International patent publication No. WO 07131767 (DSM) discloses combination of lycopene and genistein for therapy of prostate carcinoma wherein in one of

the embodiments resveratrol is preferably added such that lycopene: resveratrol range is about 1:2 to 1:3¾.

[011] In International patent publication No. WO 2004/000043 (Perani) a food supplement is disclosed with both lycopene and resveratrol as antioxidants at 1:1 ratio. Another publication No. WO 2005/107729 (Kang) disclosed a skin disorder therapeutic composition comprising lycopene plus optionally resveratrol at a ratio of about 4:1.

[012] Most commercially available preparations contain extracted lycopene as crystals which are water-insoluble and can not be efficiently absorbed in human intestinal tract. Natural lycopene is sourced from intracellular microsomes of plant cells and is similarly difficult to be absorbed directly by human body through oral intake, a problem not addressed by the prior art.

[013] While the prior art also made wide therapeutic claims which have largely been speculative, our present invention endeavours to disclose certain combination ratios of lycopene to resveratrol for therapeutic use in specific ailments including arthritis, carcinoma generally and melanoma specifically, and in mitigating hyperlipoidemia.

SUMMARY OF DISCLOSURE

[014] In the general embodiment of our invention, we disclose a dietary supplement composition comprising lycopene and resveratrol in a range of ratio of lycopene:resveratrol from 1:10 to 10:1. Preferably, the ratio is 1:2 to 1:4. In a first aspect of our composition, the lycopene is preferably of ≥95% purity and resveratrol is of ≥98% purity. Both lycopene and resveratrol may preferably comprise of nano-sized particles. Preferably, the particles are in the form of crystal powder to optimize intestinal absorption upon oral intake in the form of capsule or tablet. In small dosage, it should preferably include a minimum of 5 mg of lycopene and 10 mg of resveratrol.

[015] In a second aspect of our composition, various range of ratios of lycopene:resveratrol are provided for specific therapeutic purposes including 1:4 for symptomatic relief of arthritis, 1:2 for inhibiting melanoma or carcinoma malignancy, and 1:3 for inhibiting hyperlipoidemia. Generally, our dietary supplement composition may be used as an agent for anti-ageing, anti-oxidative, inhibiting development of cardiovascular diseases, relieving menopause symptoms and remission of post-operative cancer patients.

LIST OF ACCOMPANYING DRAWINGS

[016] The drawings accompanying this specification as listed below may provide a better understanding of our invention and its advantages when referred in conjunction with the detailed description the follows as exemplary and non-limiting embodiments of our composition, in which:

[017] FIGURE 1: is a column chart showing pain index of arthritis patients in placebo group, group treated with resveratrol only, group treated with lycopene only and group treated with combination of both resveratrol and lycopene;

[018] FIGURE 2 is a line graph illustrating growth of melanoma graft in nude mice: untreated control, treated only with resveratrol, treated only with lycopene and combination of both resveratrol and lycopene;

[019] FIGURE 3 is a column chart showing triglycerides levels in untreated control group, group treated with resveratrol only, group treated with lycopene only and group treated with combination of both resveratrol and lycopene.

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

[020] Our new composition is formulated based on the results of our research over years which revealed synergistic and complementary effects of the two potent anti-oxidative compounds, i.e. lycopene and resveratrol, as active ingredients. One main aspect of our findings concerns the bioavailability of these two compounds upon oral intake, and their respective distribution or deposition upon uptake in the human body.

[021] After oral intake, over 90 percent of lycopene that is able to be adsorbed goes to the prostate and other internal organs while resveratrol is mainly distributed in the heart, circulation system, along respiratory tract and skin. From the following trials and results, it may be shown that the combination of the two compounds appears to show synergistic effects and to possess significantly higher activities in mitigating a number of diseases and malignancies and in improving conditions of some disorders than those of each of the compounds on its own.

[022] In the broad, general embodiment of our dietary supplement composition, lycopene and resveratrol are to be admixed in a range of ratio of lycopene:resveratrol from 1:10 to 10:1 with the range of 1:2 to 1:4 considered as optimal ratio.

[023] The bio-absorption of the two compounds following oral intake may be increased with the compounds provided in a certain high levels of purity and specific microscopic structural form. [By "microscopic" we mean particle size of a scale lower than micrometer, i.e. including nanometer and Å scale.]

[024] Lycopene is preferably provided in purity ≥95% while resveratrol is preferably provided in purity ≥98%. Both compounds are also preferably provided in form of nano-sized particles, particularly micro-crystalline particles, or nano-crystals. These microscopic crystalline forms of lycopene and resveratrol may be produced with suitable conventional controlled recrystallization techniques such as single or multi-solvent solvent recrystallization, hot filtration recrystallization, and seeding, or a proprietary technology such as Elan Pharmaceutical's *NanoCrystal*™ technology for synthesizing nano-scale crystals optimized for water-solubility.

[025] Examples of preparation of the composition comprising lycopene and resveratrol in various ratio are given in the following:

[026] Preparation Example 1 – lycopene : resveratrol composition in 1:2 ratio. 100 grams of lycopene with a purity of 95% and 200 g of resveratrol with a purity of 98% were mixed and sieved through a 100-mesh filter. The mixture was then capsulated, yielding a total of 1580 capsules with an average weight

of 190 mg each.

[027] Preparation Example 2 – lycopene : resveratrol composition in 1:1 ratio. 200 g of lycopene with a purity of 95% and 200 g of resveratrol with a purity of 98% were mixed and sieved through a 100-mesh filter. The mixture was then capsulated, yielding a total of 2000 capsules, averaging 200 mg each.

[028] Preparation Example 3 – lycopene : resveratrol composition in 2:1 ratio. 200g of lycopene with a purity of 95% and 100g of resveratrol with a purity of 98% were mixed and sieved through a 100-mesh filter. The mixture was then capsulated, yielding a total of 1200 capsules, averaging 250mg each.

For smaller dosages, our dietary supplement may be formulated as having, for example, 5 mg of lycopene and 10 mg of resveratrol in a 15 mg capsule or tablet. Conventional methods may be employed to make tablets such as the use of binding agent such as starch and/or magnesium stearate. For an example of lycopene : resveratrol composition in 1:3 ration 100 grams of lycopene with a purity of 95% and 300 g of resveratrol with a purity of 98% may be mixed with 40 g starch, and then mixed with 200 g starch slurry before tablet-making.

[029] The second major aspect of our present invention concerns certain combination ratios of lycopene to resveratrol for therapeutic use in specific

ailments including arthritis, carcinoma generally and melanoma specifically, and in mitigating hyperlipoidemia.

TRIAL 1 – Symptomatic relief of arthritis

[030] Forty subjects chosen for having a history of over 10 years suffering from knee joints pain. They were divided into 4 groups. Each group was served with placebo capsules, resveratrol (e.g. 400 mg/person/day) or lycopene (e.g. 100 mg/person/day), or the combination of both, respectively as indicated in FIGURE 1. Five grades (as pain index) were designed for patients to define their painfulness.

[031] Upon completion of the trial, they experienced complete relief or near complete relief from knee joint pain within one month. The best daily dose is speculated to be 100 mg of lycopene and 400 mg of resveratrol, i.e. lycopene : resveratrol in the ratio of 1:4 for efficacious symptomatic relief of arthritis. As is apparent from the bar chart of FIGURE 1, the combination of resveratrol and lycopene showed synergistic effect on providing symptomatic relief of rheumatic knee joint pain.

TRIAL 2 – Inhibition of melanoma malignancy

[032] Inhibition of melanoma growth is shown in FIGURE 2 where the

subjects are C57 mouse which are grafted with B16 murine melanoma tumour cells. From the line graph of FIG. 2, it is apparent that the combination of both lycopene and resveratrol has synergistic effect in suppressing growth of melanoma grafts. The optimal ratio of lycopene: resveratrol is suggested to be in the range of 1:2 for efficacious suppression of growth of carcinoma including melanoma.

[033] In one specific case, a man with a tonsil tumor sized 3 × 3 cm, reported shrinkage of the tumor a size below the detectable range of magnetic resonance imaging after three-month intake of our dietary supplement comprising lycopene and resveratrol according to the aforesaid ratio. As is apparent from the bar chart of FIGURE 2, the combination of resveratrol and lycopene showed synergistic effect in suppressing growth of tumor.

TRIAL 3 – Lowering of triglyceride levels in hyperlipoidemia

[034] Forty volunteer patients with hyperlipoidemia or having symptoms of high levels of triglyceride were enrolled in a one-month experiment. They were divided into 4 groups, and each group was given a different formulation of lycopene and/or resveratrol or none (control). The results are shown in FIGURE 3. The group taking 600 mg resveratrol plus 200 mg lycopene achieved complete relief of hyperlipoidemia. Accordingly, the composition

of these 2 phytochemicals in the ratio of lycopene : resveratrol at 1:3 may be considered optimal for inhibiting hyperlipoidemia. The combination of resveratrol and lycopene showed synergistic effect in lowering the level of triglycerides in blood.

[035] Further health promoting effects of our preparation of lycopene and resveratrol may be expected to include anti-ageing, anti-oxidative, inhibiting cardiovascular diseases, relieving menopause symptoms and remission of post-operative cancer patients.

[036] It would be apparent to a person skilled in the art that the suggested methods of obtaining the 2 active ingredients, i.e. lycopene and resveratrol, in their respective purity and nano-crystalline form may be obtained from alternative or modified techniques. The aforementioned ratios of lycopene and resveratrol are suggestive based on our trial results and the respective experimental conditions and may be subject to variance or tolerances. Many of the formulation or dosage techniques described above may also be similarly achieved with other conventional methods known to the notional skilled person. These modifications, adaptations and alternatives are to be considered as equivalents to our invention and fall within the scope and letter of the following claims.

LIST OF REFERENCES

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CLAIMS

1. A dietary supplement composition comprising lycopene and resveratrol in a range of ratio of lycopene : resveratrol from 1:10 to 10:1.

2. A dietary supplement composition according to Claim 1 wherein the ratio is 1:2 to 1:4.

3. A dietary supplement composition according to Claim 1 wherein the lycopene is of ≥95% purity.

4. A dietary supplement composition according to Claim 3 wherein the lycopene comprises nano-sized particles.

5. A dietary supplement composition according to Claim 4 wherein the lycopene comprises crystal powder.

6. A dietary supplement composition according to Claim 1 wherein the resveratrol is of ≥98% purity.

7. A dietary supplement composition according to Claim 6 wherein the resveratrol comprises nano-sized particles.

8. A dietary supplement composition according to Claim 7 wherein the resveratrol comprises crystal powder.

9. A dietary supplement composition according to Claim 2 comprising lycopene:resveratrol in the range of 1:4 for symptomatic relief of arthritis.

10. A dietary supplement composition according to Claim 2 comprising lycopene:resveratrol in the range of 1:2 for inhibiting carcinoma malignancy.

11. A dietary supplement composition according to Claim 10 for inhibiting melanoma malignancy.

12. A dietary supplement composition according to Claim 2 comprising lycopene:resveratrol in the range of 1:3 for inhibiting hyperlipoidemia.

13. A dietary supplement composition according to any one of Claims 9 to 12 wherein the lycopene and resveratrol act synergistically.

14. A dietary supplement composition according to any one of Claims 1 – 8 formulated for oral intake.

15 A dietary supplement composition according to Claim 14 formulated in a capsule or tablet.

16. A dietary supplement composition according to Claim 15 comprising at least 5 mg of lycopene and 10 mg of resveratrol.

17 A dietary supplement composition according to Claim 15 formulated in a capsule or tablet form comprising a unit weight of a range taken from 190 to 400 mg.

18. A dietary supplement composition according to any one of Claims 1 - 12 for use as an agent for anti-ageing, anti-oxidative, inhibiting development of cardiovascular diseases, relieving menopause symptoms and remission of post-operative cancer patients.