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(54) Title: COMPOSITION COMPRISING PHYTOSTEROLS AND KUDZU AND ITS USE IN THE TREATMENT, ALLEVIATION OR PREVENTION OF METABOLIC DISORDERS

(57) Abstract: Composition comprising phytosterols and Kudzu and its use in the treatment, alleviation or prevention of metabolic disorders and disorders associated therewith. The metabolic disorders are associated with hypertriglyceridemia, overweight, obesity, diabetes, hypertension, liver cirrhosis, metabolic syndrome and combinations thereof. Kudzu is provided as kudzu root, kudzu leaf, kudzu flower, dried kudzu or as an extract thereof.



**COMPOSITION COMPRISING PHYTOSTEROLS AND KUDZU  
AND ITS USE IN THE TREATMENT, ALLEVIATION OR  
PREVENTION OF METABOLIC DISORDERS**

The present invention generally relates to the field of health and wellness. In particular, the present invention addresses metabolic disorders and disorders associated therewith. For example, the present invention describes a composition comprising phytosterols and Kudzu for use in the treatment, alleviation or prevention of metabolic disorders.

During the past decades, the prevalence of obesity has increased worldwide to epidemic proportion. Approximately 1 billion of people worldwide are overweight or obese, conditions that increase mortality, mobility and economical costs. Obesity develops when energy intake is greater than energy expenditure, the excess energy being stored mainly as fat in adipose tissue. Body weight loss and prevention of weight gain can be achieved by reducing energy intake or bioavailability, increasing energy expenditure and /or reducing storage as fat. Obesity represents a serious threat to health because it is associated with an array of chronic diseases, including diabetes, atherosclerosis, degenerative disorders, airway diseases and some cancers.

Kudzu and phytosterols are well known to have beneficial health effects; however, both individual ingredients have their limitations.

Kudzu (Radix Pueraria) is a rich source of isoflavone glucosides, has traditional been used to treat alcoholism, diabetes, gastroenteritis, and deafness. The most abundant isoflavone of kudzu is puerarin (daidzein 8-C-glucoside). Its  
5 compound also contains daidzein, daidzin (daidzei 7-O-glucoside) and other isoflavones. An initial observation was that the puerarin lowered apolipoprotein (ApoB100) secretion in liver cells but not intestinal cell line (Lee et al., 2002 (Lee JS, et al., *BMC Complement Altern Med.* 2002 Dec 16;2:12.  
10 Epub 2002.

While Kudzu generally is accepted as safe to administer, in very rare cases unwanted side effects have been reported. These may range from allergic reactions after oral consumption to slowing blood clotting and possible interference with other  
15 medical treatments.

Hence, as a matter of precaution, it is advisable to keep kudzu dosages as low as possible.

When administered at low dosages in order to avoid such exceptional unwanted side effects kudzu was found to have no  
20 statistically significant effect on blood lipids, or cholesterol reduction.

Phytosterols are known to be able to reduce blood concentrations of total and LDL cholesterol by reducing

cholesterol absorption in the gut. A daily intake of around 2.4 g of plant sterols (or its saturated form, stanols) is associated with an 8% reduction of blood total cholesterol concentrations. There are also some indications that phytosterols might have an effect on diabetes (Five Phytosterols from Aloe Vera Gel as Anti-diabetic Compounds; Tanaka et al., Biological and Pharmaceutical Bulletin Vol. 29 (2006), No. 7 1418). However, if administered in significant amounts, phytosterols may have unwanted side effects. For example, they are known to inhibit alpha and beta carotene absorption. Beta carotene is an important source of Vitamin A which is essential, e.g., for growth and development.

When administered at low dosages that avoid significant unwanted side effects plant sterols have no statistical significant effect on metabolic disorders such as obesity.

However, there is a clear need in the art for natural preparations that can be safely used without side effects and that allow reducing the risk for developing metabolic disorders.

The present inventors have addressed this need.

Consequently, it was the objective of the present invention to improve the state of the art and - in particular - to provide

a natural composition that overcomes the problems of the prior art and addresses the needs described above.

The present inventors were surprised to see that the subject matter of the independent claim achieves the objective of the present invention. The subject matter of the dependant claims further develops the central idea of the present invention.

In particular, the inventors have found in a hamster model that - when administered together - kudzu and phytosterols act synergistically and allow reducing blood lipids, body weight gain and fat buildup statistically significant, while keeping the individual dosages of phytosterols and kudzu sufficiently low to avoid unwanted side effects and discomfort.

Consequently, the present invention relates in part to a composition comprising phytosterols and kudzu for use in the treatment, alleviation or prevention of metabolic disorders.

The present invention also relates to the use of phytosterols and kudzu in the preparation of a composition for treating, alleviating or preventing metabolic disorders.

The combination of kudzu and phytosterols was shown to be very effective in prevention the build-up of high blood lipid concentrations in particular when consuming a high-fat diet.

For the purpose of the present invention is a diet to be considered "high-fat", if its fat content is at least 10%, at least 25%, at least 50%, at least 75% or at least 100% above the daily recommended intake (RDI).

- 5 Consequently, the metabolic disorder that can be prevented, ameliorated or treated with the composition of the present invention may be associated with hypertriglyceridemia.

For example, the metabolic disorder may be selected from the group consisting of overweightness, obesity, diabetes,  
10 hypertension, liver cirrhosis, metabolic syndrome and combinations thereof.

"Overweight" is defined for an adult human as having a BMI between 25 and 30.

"Body mass index" or "BMI" means the ratio of weight in kg  
15 divided by the height in metres, squared.

"Obesity" is a condition in which the natural energy reserve, stored in the fatty tissue of animals, in particular humans and other mammals, is increased to a point where it is associated with certain health conditions or increased  
20 mortality. "Obese" is defined for an adult human as having a BMI greater than 30.

Of particular importance are for the potential development of further metabolic disorders are high body weights, in particular an elevated fat mass.

Consequently, the prevention or treatment of overweightness  
5 and/or obesity is an important application of the present invention.

The inventors could demonstrate that the composition of the present invention could be used to prevent or reduce the accumulation of excessive amounts of perirenal fat.

10 Hence, the composition of the present invention may be for use in reducing or preventing an increase of the perirenal fat to body weight ratio.

This is in particular useful, when high-fat diets are consumed.

Perirenal fat thickness is also an independent predictor of  
15 chronic kidney disease, increased renal resistance index and hyperuricaemia in type-2 diabetic patients (Iamacchia et al., Nephrol. Dial. Transplant. (2011) 26 (3): 892-898).  
Consequently, the composition of the present invention may be used in the treatment of prevention of these disorders as well.

20 The inventors have also found that the composition of the present invention can very well be used to prevent or reduce the build-up of abdominal fat.

Hence, the composition may be for use in reducing or preventing an increase of the abdominal fat to body weight ratio.

Abdominal fat may be visceral fat surrounding the abdominal  
5 organs or subcutaneous located in between the skin and the abdominal wall.

The composition of the present invention has an effect on visceral fat and on subcutaneous fat.

While it is well known that that visceral fat is the main fat  
10 deposit that is correlated with risk factors such as insulin resistance, recent results also suggests that subcutaneous fat may also be involved in such risk factors, in particular in men (Goodpaster et al., Diabetes, October 1997, vol. 46 no. 10 1579-1585).

15 The relationship of obesity to the risk for developing non-insulin-dependent diabetes mellitus (NIDDM), hypertension, and cardiovascular diseases is meanwhile well established (Smith et al., Metabolism, Vol 50, No 4 (April), 2001: pp 425-435); consequently, the composition of the present invention may be  
20 used to treat or prevent these disorders as well.

Also for individuals who are not suffering from metabolic disorders, the compositions of the present invention may be

useful. They may for example be used to support weight management.

Weight management may be beneficial to maintain or improve an individual's satisfaction with its appearance and wellness.

- 5 Weight management may also be seen as preventive measure to reduce the risk of getting metabolic disorders.

Hence, the composition of the present invention may be for use in the support of weight management.

In therapeutic applications, compositions are administered in  
10 an amount sufficient to at least partially cure or arrest the symptoms of a disease and/or its complications. An amount adequate to accomplish this is defined as "a therapeutically effective dose". Amounts effective for this purpose will depend on a number of factors known to those of skill in the  
15 art such as the severity of the disease and the weight and general state of the patient.

In prophylactic applications, compositions according to the invention are administered to a patient susceptible to or otherwise at risk of a particular disease in an amount that is  
20 sufficient to at least partially reduce the risk of developing a disease. Such an amount is defined to be "a prophylactic effective dose". Again, the precise amounts depend on a number

of patient specific factors such as the patient's state of health and weight.

The compositions of the present invention are effective following a dose-response curve. They may be administered in a therapeutically effective dose or a prophylactic effective dose. Skilled artisans will be able to determine such dosages appropriately.

However, generally the composition of the present invention may be administered in a daily dose corresponding to at least 0.04 g, 0.6 g, 3 g, 6 g, 10 g, or 80 g kudzu and at least 2.5 mg, 10 mg, 15 mg, 25 mg, or 40 mg phytosterols per kg body weight per day.

For example, the composition of the present invention may comprise at least 0.04 g kudzu and at least 2.5 mg phytosterols per kg body weight per day.

Alternatively, the composition of the present invention may comprise at least 3 g kudzu and at least 15 mg phytosterols per kg body weight per day.

Further alternatively, the composition of the present invention may comprise at least 6 g kudzu and at least 40 mg phytosterols per kg body weight per day.

To avoid unwanted side effects such as off-tastes or inhibitions of vitamin A absorptions, the dosages should be kept at a reasonably low level.

For example, the dosages of kudzu may not exceed 6 g per kg  
5 body weight per day and the dosage of phytosterols may not exceed 40 mg per kg body weight per day.

Kudzu may be provided in any form suitable for administration to humans or animals. For example, kudzu may be provided as kudzu root, kudzu leaf, kudzu flower, dried kudzu or as an  
10 extract thereof.

The extract may be for example a watery extracts. Watery extracts have the advantage that no solvents must be removed from the extract before the extract can be used for human or animal consumption.

15 Typical phytosterols that may be used for the purpose of the present invention may be selected from the group consisting of plant sterols, stanols, or combinations thereof.

Examples are  $\beta$ -sitosterol, campesterol and/or stigmasterol.

Phytosterols may be provided as chemically pure compounds. As  
20 such they may be purified from plant sources or synthesized chemically. This allows a very precise dosing.

It may also be preferred to provide phytosterols from natural sources or extracts thereof. As such the phytosterols may be dietary phytosterols. They may be provided as vegetable oils, nuts, cereal products, vegetables, fruit, berries or as  
5 extracts thereof.

The composition may be any composition that is suitable for human or animal consumption.

As such the composition may be selected from the group consisting of a food product, a drink, a functional food, a  
10 nutraceutical, a food additive, a nutritional formula, and a pet food product.

As metabolic disorders not only occur in humans but also in animals the composition of the present invention may be to be administered to humans or animals, for example companion  
15 animals such as cats or dogs.

Advantageously, the composition of the present invention may be consumed briefly before, with or briefly after the consumption of a high-fat meal.

As such, the composition may be to be administered in the time  
20 frame from 1 hour before to 1 hour after a high fat meal.

Those skilled in the art will understand that they can freely combine all features of the present invention described herein,

without departing from the scope of the invention as disclosed. In particular, features described for the uses of the present invention may be applied to the composition of the present invention and vice versa.

5 Further advantages and features of the present invention are apparent from the following Examples and Figures.

Figure 1 shows that the combination treatment of Kudzu and plant sterols at the same dose significantly and synergistically caused a robust reduction in perirenal fat  
10 gain in HFD hamsters. Data were analyzed by one-way ANOVA followed by Tukey's multiple comparison tests and unpaired student t test. Mean $\pm$ SEM, n=8-12, \*P<0.05, versus control; †P<0.05, versus HFD placebo.

Figure 2 shows that the combination treatment of Kudzu and  
15 plant sterols at the same dose significantly and synergistically caused a robust reduction in abdominal fat gain in HFD hamsters. Data were analyzed by one-way ANOVA followed by Tukey's multiple comparison tests and unpaired student t test. Mean $\pm$ SEM, n=8-12, \*P<0.05, versus control;  
20 †P<0.05, versus HFD placebo.

Examples

Golden Syrian hamsters weighing about 120-130g were purchased from Beijing Vital River Laboratory Animal Co.,Ltd. Animals were housed in a controlled environment (22-24°C and 12h light-12h dark) with free access to tap water and food.

5 After 1 week of acclimatization, hamsters were randomly allocated to different test groups. Hyperlipidemia was induced by feeding the animals a diet high in cholesterol and determined by the elevated plasma TC, TG and HDL-C level. The diet was prepared by mixing the following ingredients (g/kg):

|    |                     |                      |
|----|---------------------|----------------------|
| 10 | Formula             | High-fat Diet (g/kg) |
|    | Cholesterol         | 1                    |
|    | Cornstarch          | 508                  |
|    | Casein              | 242                  |
|    | Lard                | 150                  |
| 15 | sucrose             | 119                  |
|    | DL-methionine       | 1                    |
|    | Vitamin Mix AIN-76A | 20                   |
|    | Mineral Mix AIN-76  | 40                   |

The ingredient powders were mixed with a gelatin solution  
 20 (20g/L) in a ratio of 200g diet per liter of solution. Once the gelatin had set, the diets were cut into pieces of approximately 10g cubes and stored frozen at -80C until use.

The test groups were the following:

- 1) Control: Normal Diet group (n=12)
- 2) HFD: High Fat Diet group (n=12)
- 3) HFD-K: Kudzu root extraction in High Fat Diet (3g/kg/day, n=12)
- 5 4) HFD-PS: plant sterol esters in High Fat Diet (plant sterol esters 0.15g/kg/day, n=12)
- 5) HFD-PS/K: plant sterol esters and Kudzu extract in High Fat Diet (n=12)

1. Synergistic effect of phytosterols (PS) and Kudzu Root (K)  
10 on Fat Tissue reduction.

Excessive body weight is associated with various diseases, particularly cardiovascular diseases, diabetes mellitus type 2, obstructive sleep apnea, certain types of cancer, and osteoarthritis. As a result, obesity has been found to reduce  
15 life expectancy.

1.1 Perirenal Fat: After 8 weeks of treatment, high fat diet significantly elevated the perirenal fat to body weight ratio (Table 1, HFD-Placebo vs. control). Simultaneous Treatment with either plant sterols or a kudzu root water extract alone  
20 had no significant alteration effect on body weight compared with HFD placebo (Fig 1, HFD-K, HFD-PS vs. control, \*P<0.05;

HFD-K, HFD-PS vs. HFD-Placebo,  $P>0.05$ ). Although the two individual ingredients did not show the significant protection effect *alone*, the combination treatment of kudzu root and plant sterol at the same dose significantly reduced the perirenal fat to body weight ratio compared with HFD-placebo (Fig 1, HFD-PS/K vs. HFD placebo,  $\dagger P<0.05$ ).

Table 1. Perirenal Fat reduction effect of Kudzu root (K) water extract and phytosterols (PS) in a high fat diet (HFD) hamster.

|                                        | Control         | HFD-placebo        | HFD-K              | HFD-PS             | HFD-K/PS                |
|----------------------------------------|-----------------|--------------------|--------------------|--------------------|-------------------------|
| Perirenal Fat/Body Weight Ratio (mg/g) | $5.89 \pm 0.56$ | $15.49 \pm 0.87^*$ | $13.27 \pm 1.08^*$ | $13.05 \pm 0.14^*$ | $12.3 \pm 0.63^\dagger$ |

1.2 Abdominal Fat: After 8 weeks of treatment, the high fat diet significantly elevated the abdominal fat and abdominal fat to body weight ratio (Table 2, HFD-Placebo vs. control). Simultaneous treatment with either phytosterols or kudzu root water extract had no significant alteration effect on body weight compared with HFD placebo (Fig 2, HFD-K, HFD-PS vs. control,  $*P<0.05$ ; HFD-K, HFD-PS vs. HFD-Placebo,  $P>0.05$ ). Although the two individual ingredients did not show a significant protection effect *alone*, the combination treatment of kudzu root and plant sterol at the same dose significantly

reduced the abdominal fat to body weight ratio compared with HFD-placebo (Fig 2, HFD-PS/K vs. HFD placebo, †P<0.05).

Table 2. Abdominal fat reduction effect of Kudzu root (K) water extract and phytosterols (PS) in a high fat diet (HFD) hamster.

|                                 | Control      | HFD-placebo   | HFD-K         | HFD-PS        | HFD-K/PS      |
|---------------------------------|--------------|---------------|---------------|---------------|---------------|
| Abdominal Fat/Body Weight Ratio | 16.67 ± 1.01 | 27.12 ± 1.23* | 24.57 ± 1.13* | 23.78 ± 0.84* | 23.54 ± 1.40† |

**Claims:**

1. Composition comprising phytosterols and Kudzu for use in the treatment, alleviation or prevention of metabolic disorders.
- 5 2. Composition for use in accordance with claim 1, wherein the metabolic disorder is associated with hypertriglyceridemia.
3. Composition for use in accordance with one of the preceding claims, wherein the metabolic disorder is  
10 selected from the group consisting of overweightness, obesity, diabetes, hypertension, liver cirrhosis, metabolic syndrome and combinations thereof.
4. Composition for use in accordance with one of the preceding claims to reduce or prevent an increase of the  
15 perirenal fat to body weight ratio.
5. Composition for use in accordance with one of the preceding claims to reduce or prevent an increase of the abdominal fat to body weight ratio.
6. Composition for use in accordance with one of the  
20 preceding claims to support weight management.

7. Composition for use in accordance with one of the preceding claims wherein the composition is to be administered in a daily dose corresponding to at least 0.04g, 0.6 g, 3 g, 6 g, 10 g, or 80g kudzu and at least  
5 2.5 mg, 10 mg, 15 mg, 25 mg, or 40 mg phytosterols per kg body weight per day.

8. Composition for use in accordance with one of the preceding claims wherein wherein kudzu is provided as kudzu root, kudzu leaf, kudzu flower, dried kudzu or as an  
10 extract thereof.

9. Composition for use in accordance with claim 8, wherein the extract is a watery extract.

10. Composition for use in accordance with one of the preceding claims wherein the phytosterols are selected  
15 from the group consisting of plant sterols and stanols; for example  $\beta$ -sitosterol, campesterol and stigmasterol.

11. Composition for use in accordance with one of the preceding claims wherein the phytosterols are dietary phytosterols and are provided as vegetable oils, nuts, cereal products, vegetables, fruit and berries or as  
20 extracts thereof.

12. Composition for use in accordance with one of the preceding claims wherein the composition is selected from the group consisting of a food product, a drink, a functional food, a nutraceutical, a food additive, a nutritional formula, and a pet food product.

13. Composition for use in accordance with one of the preceding claims wherein the composition is to be administered to adults or the elderly.

14. Composition for use in accordance with one of the preceding claims wherein the composition is to be administered to humans or animals, for example companion animal such as cats or dogs.

15. Composition for use in accordance with one of the preceding claims wherein the composition is to be administered in the time frame from 1 hour before to 1 hour after a high fat meal.

Figure 1:

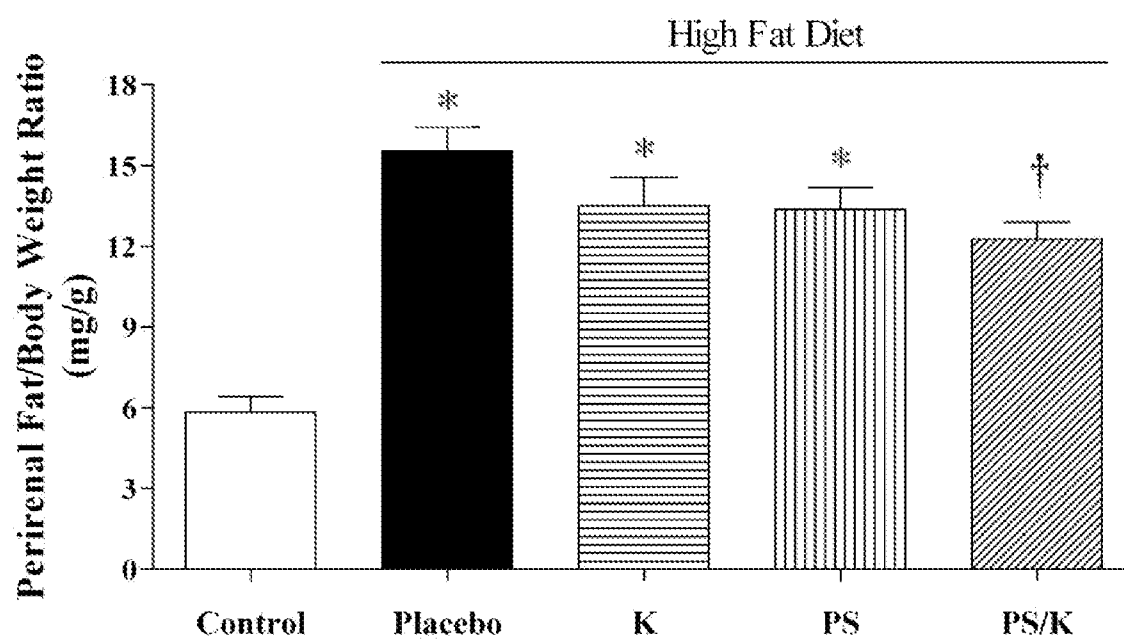
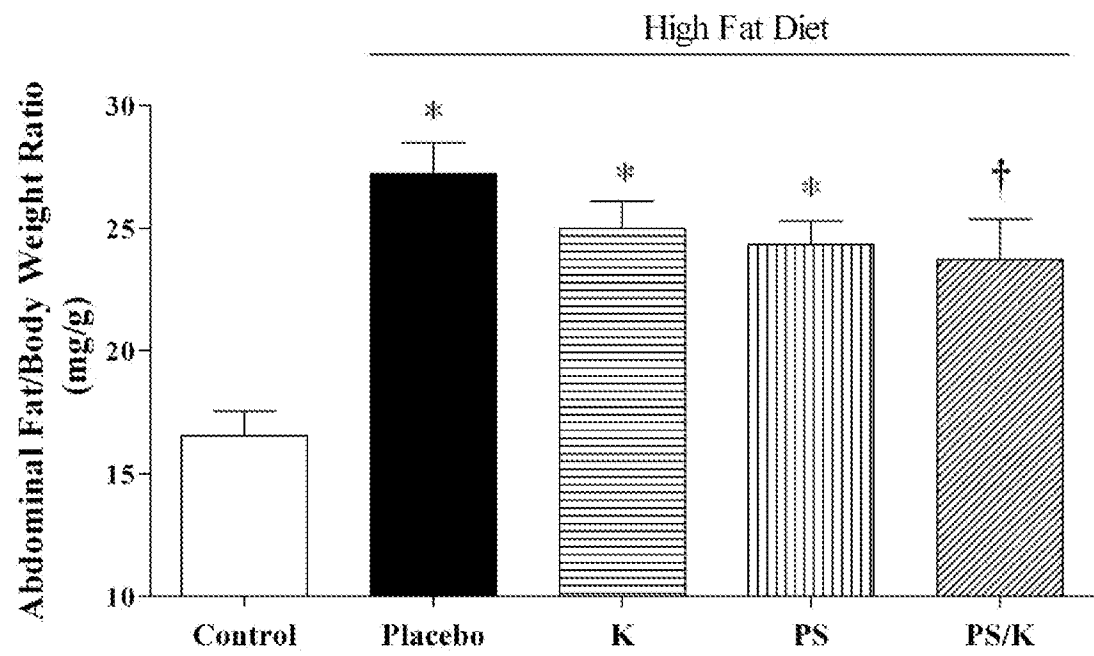


Figure 2:



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2012/079048

**A. CLASSIFICATION OF SUBJECT MATTER**

See the extra sheet

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 A 61K, A61P

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 practicable, search terms used)

WPI, EPODOC, CNPAT, CNKI, PUERARIA, KUDZU, KUDZUVINE, PUERARIAE, PHYTOSTEROL, PLANT STEROL, PLANT STANOL, SOYBEAN STEROL, SITOSTEROL, CAMPESTEROL, STIGMASTEROL, METABOLIC, OVER WEIGHT, OBESITY, DIABETES, HYPERTENSION, LIVER CIRRHOSIS, HYPERTRIGLYCERIDEMIA, ABDOMINAL FAT, PERIRENAL FAT

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------|-----------------------|
| X         | KR20070106304A(SAMYANG GENEX CORP), 01 Nov. 2007(01.11.2007), see abstract         | 1-15                  |

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

|                                                                                                                                                                          |                                                                                                                                                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| * Special categories of cited documents:                                                                                                                                 | “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                                              |
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|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Date of the actual completion of the international search<br>12 Apr. 2013(12. 04. 2013)                                                                                                                      | Date of mailing of the international search report<br><b>25 Apr. 2013 (25.04.2013)</b> |
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## A. CLASSIFICATION OF SUBJECT MATTER

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