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Declarations under Rule 4.17:

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- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
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(54) Title: HAWTHORN AND PHYTOSTEROLS AND THEIR EFFECT ON METABOLIC DISORDERS

(57) Abstract: 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 hawthorn for use in the treatment, alleviation or prevention of metabolic disorders.



Hawthorn and phytosterols and their effect on metabolic disorders

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

During the past decades, the prevalence of obesity has
10 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
15 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
20 diseases, including diabetes, atherosclerosis, degenerative disorders, airway diseases and some cancers.

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

25 Hawthorn a flowering shrub of the rose family. Its health benefits are for example reviewed by Rigelsky and Sweet, Am J Health Syst Pharm March 1, 2002 59:417-422. Hawthorn has an extensive history of use in cardiovascular diseases, dating back to the 1st century. It has been shown to have a promising
30 effect on blood cholesterol reduction and there are also suggestions of a beneficial effect on blood lipids.

However, to achieve biologically significant effect, daily consumption of hawthorn juice frequently causes stomach discomfort due to its acidic taste. Further, at therapeutic dosages, hawthorn may cause a mild rash, headache, sweating, dizziness, palpitations, sleepiness, agitation, and gastrointestinal symptoms (Rigelsky and Sweet, Am J Health Syst Pharm March 1, 2002 59:417-422).

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 or gut discomfort hawthorn or 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 - hawthorn 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 hawthorn sufficiently low to avoid unwanted side effects and discomfort.

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

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

The combination of hawthorn 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).

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, hypertension, liver cirrhosis, metabolic syndrome and combinations thereof.

10 "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 divided by the height in metres, squared.

15 "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 mortality. "Obese" is defined for an adult human as having a BMI greater than 30.

20 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 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.

5 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.

10 Perirenal fat thickness is also an independent predictor of 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
15 well.

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.

20 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 organs or subcutaneous located in between the skin and the abdominal wall.

25 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 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).

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 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.

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 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

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 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 0.5 g, 1 g, or 3 g hawthorn and at least at least 2.5 mg, 15 mg, or 40 mg phytosterols per kg body weight per day.

For example, the composition of the present invention may comprise at least 0.5 g hawthorn and at least 2.5 mg phytosterols per kg body weight per day.

Alternatively, the composition of the present invention may comprise at least 1 g hawthorn and at least 15 mg phytosterols per kg body weight per day.

Further alternatively, the composition of the present invention may comprise at least 3 g hawthorn 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 hawthorn may not exceed 2.5 g per kg body weight per day and the dosage of phytosterols may not exceed 40 mg per kg body weight per day.

Hawthorn may be provided in any form suitable for administration to humans or animals. For example, hawthorn may be provided as fresh fruit, dried fruit, hawthorn leaf or as an extract thereof.

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 β -sitosterol, campesterol and/or stigmasterol.

Phytosterols may be provided as chemically pure compounds. As 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 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

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
5 administered to humans or animals, for example companion 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.

10 As such, the composition may be to be administered in the time 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
15 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.

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

20 Figure 1 shows that the combination treatment of hawthorn and plant sterols at the same dose significantly and synergistically caused a robust reduction in blood triglyceride in HFD hamsters. Data were analyzed by one-way ANOVA followed by Tukey's multiple comparison tests and
25 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 hawthorn and plant sterols at the same dose significantly and

synergistically caused a robust reduction in body weight 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 3 shows that the combination treatment of hawthorn and plant sterols at the same dose significantly and synergistically caused a robust reduction in perirenal 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; †P<0.05, versus HFD placebo.

Figure 4 shows that the combination treatment of hawthorn and 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; †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.

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):

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

- 10 The ingredient powders were mixed with a gelatin solution (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:

- 15 1) Control: Normal Diet group (n=12)
- 2) HFD: High Fat Diet group (n=12)
- 3) HFD-H: Hawthorn slurry in High Fat Diet (fresh fruit 5g/kg/day, n=12)
- 4) HFD-PS: plant sterol esters in High Fat Diet (plant sterol esters 0.15g/kg/day, n=12)
- 20 5) HFD-PS/H: Hawthorn slurry and plant sterol esters in High Fat Diet (n=12)

1. Synergistic effect of plant sterol (PS) and hawthorn (H) on blood triglyceride (TG) reduction.

- 25 Background: In medicine, hypertriglyceridemia denotes high (hyper-) blood levels (-emia) of triglycerides, the most

abundant fatty molecule in most organisms. It has been associated with atherosclerosis, even in the absence of hypercholesterolemia (high cholesterol levels). It can also lead to pancreatitis in excessive concentrations (i.e. when the triglyceride concentration is greater, and often very much greater, than 1000 mg/dl or 12 mmol/l).

Blood Triglyceride: After 6 weeks of treatment, high fat diet significantly elevated the blood triglyceride by 126mg/dL (Table 1, HFD-Placebo vs. control). Plant sterol alone showed robust reduction on blood triglyceride in HFD hamsters (Fig. 1, HFD-PS vs. control, $P>0.05$; HFD-PS vs. HFD-Placebo, $\dagger P<0.05$). Although it did not show the reduction effect alone, hawthorn has enhanced the blood triglyceride reduction effect of plant sterol by 8.8mg/dL.

Table 1. Blood Triglyceride (TG) reduction effect of Hawthorn (H) and Plant Sterol (PS) in high fat diet (HFD) hamster.

	Control	HFD-placebo	HFD-H	HFD-PS	HFD-H/PS
TG (mg/dL)	131.3 $\pm$ 17.0	257.2 $\pm$ 23.2*	250.4 $\pm$ 22.8*	171.7 $\pm$ 12.8 $\dagger$	162.9 $\pm$ 17.5 $\dagger$

2. Synergistic effect of phytosterols (PS) and hawthorn (H) on body weight and fat tissue reduction.

Background: 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 life expectancy.

2.1 Body Weight: After 8 weeks of treatment, the high fat diet significantly elevated the body weight by 45.6g (Table 2, HFD-Placebo vs. control). Treatment with plant sterol or hawthorn has no significant alteration on body weight comparing with HFD placebo (Fig 2, HFD-H, HFD-PS vs. control, *P<0.05; HFD-H, HFD-PS vs. HFD-Placebo, P>0.05). Although two individual ingredients did not show the significant protection effect *per se*, the combination treatment of hawthorn and plant sterol at the same dose significantly reduced body weight comparing with HFD-placebo (Fig3.1, HFD-PS/H vs. HFD placebo, †P<0.05). In addition, the combination treatment showed synergistic reduction effect on body weight versus individual treatment (Table 2).

Table 2. Body Weight reduction effect of Hawthorn (H) and Plant Sterol (PS) in high fat diet (HFD) hamster.

	Control	HFD-placebo	HFD-H	HFD-PS	HFD-H/PS
Body Weight (g)	115.7±2.74	161.3±7.3*	157.8±3.58*	153.4±3.13*	147.2±3.84†

2.2 Perirenal Fat: After 8 weeks of treatment, the high fat diet significantly elevated the perirenal fat to body weight ratio (Table 3, HFD-Placebo vs. control). Treatment with plant sterol or hawthorn has no significant alteration on body weight comparing with HFD placebo (Fig 3, HFD-H, HFD-PS vs. control, *P<0.05; HFD-H, HFD-PS vs. HFD-Placebo, P>0.05). Although two individual ingredients did not show the significant protection effect *per se*, the combination treatment of hawthorn and plant sterol at the same dose significantly reduced perirenal fat to body weight ratio comparing with HFD-placebo (Fig 3, HFD-PS/H vs. HFD placebo, †P<0.05).

Table 3. Perirenal Fat reduction effect of Hawthorn (H) and Plant Sterol (PS) in high fat diet (HFD) hamster.

	Control	HFD-placebo	HFD-H	HFD-PS	HFD-H/PS
Perirenal Fat/Body Weight Ratio (mg/g)	5.89±0.56	15.49±0.87*	14.34±0.93*	13.05±0.14*	12.4±0.15†

2.3 Abdominal Fat: After 8 weeks of treatment, high fat diet significantly elevated the abdominal fat and abdominal fat to body weight ratio (Table 4, HFD-Placebo vs. control). Treatment with plant sterol or hawthorn has no significant alteration on body weight comparing with HFD placebo (Fig 4, HFD-H, HFD-PS vs. control, *P<0.05; HFD-H, HFD-PS vs. HFD-Placebo, P>0.05). Although two individual ingredients did not show the significant protection effect *per se*, the combination treatment of hawthorn and plant sterol at the same dose significantly reduced the abdominal fat to body weight ratio comparing with HFD-placebo (Fig 4, HFD-PS/H vs. HFD placebo, †P<0.05).

Table 4. Abdominal Fat reduction effect of Hawthorn (H) and Plant Sterol (PS) in high fat diet (HFD) hamster.

	Control	HFD-placebo	HFD-H	HFD-PS	HFD-H/PS
Abdominal Fat/Body Weight Ratio	16.67±1.01	27.12±1.23*	26.08±1.04*	23.78±0.84*	22.15±1.25†

Claims:

1. Composition comprising phytosterols and hawthorn 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 0.5 g, 1 g, or 3 g hawthorn and at least 2.5 mg, 15 mg,
25 or 40 mg phytosterols per kg body weight per day.
8. Composition for use in accordance with one of the preceding claims wherein hawthorn is provided as fresh

fruit, dried fruit, hawthorn leaf or as an extract thereof.

- 5 9. Composition for use in accordance with one of the preceding claims wherein the phytosterols are selected from the group consisting of plant sterols and stanols; for example β -sitosterol, campesterol and stigmasterol.
- 10 10. 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 extracts thereof.
- 15 11. 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.
- 20 12. Composition for use in accordance with one of the preceding claims wherein the composition is to be administered to adults or the elderly.
- 25 13. 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.
14. 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:

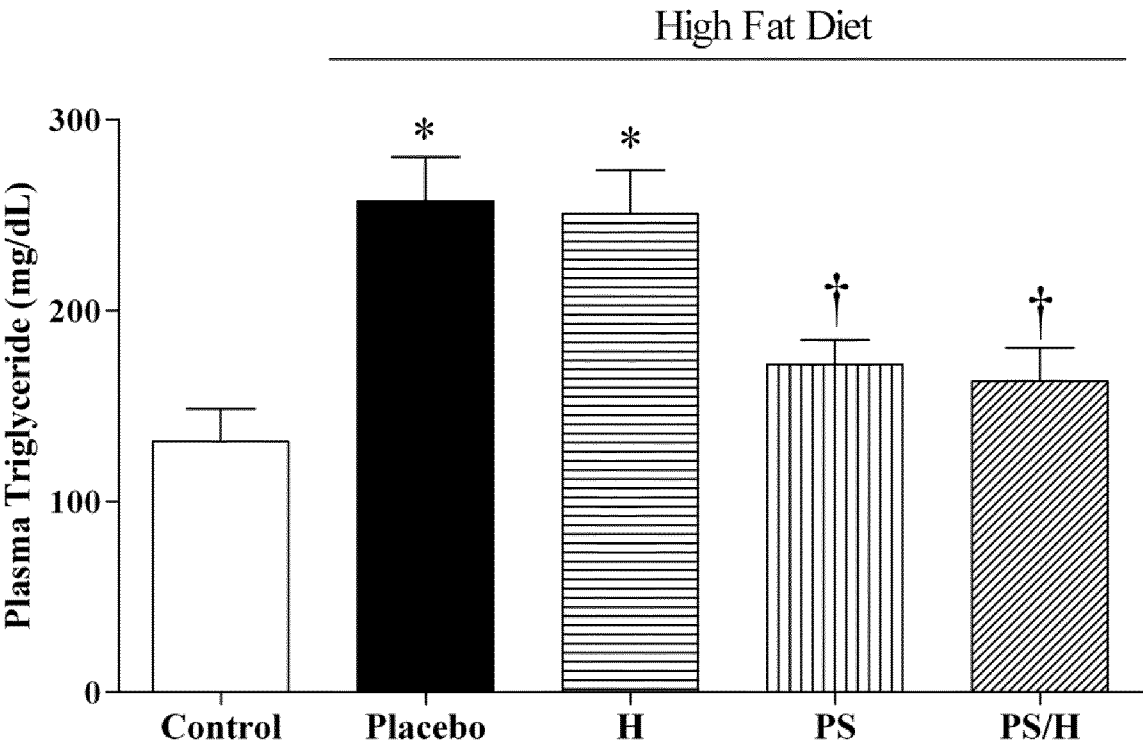


Figure 2:

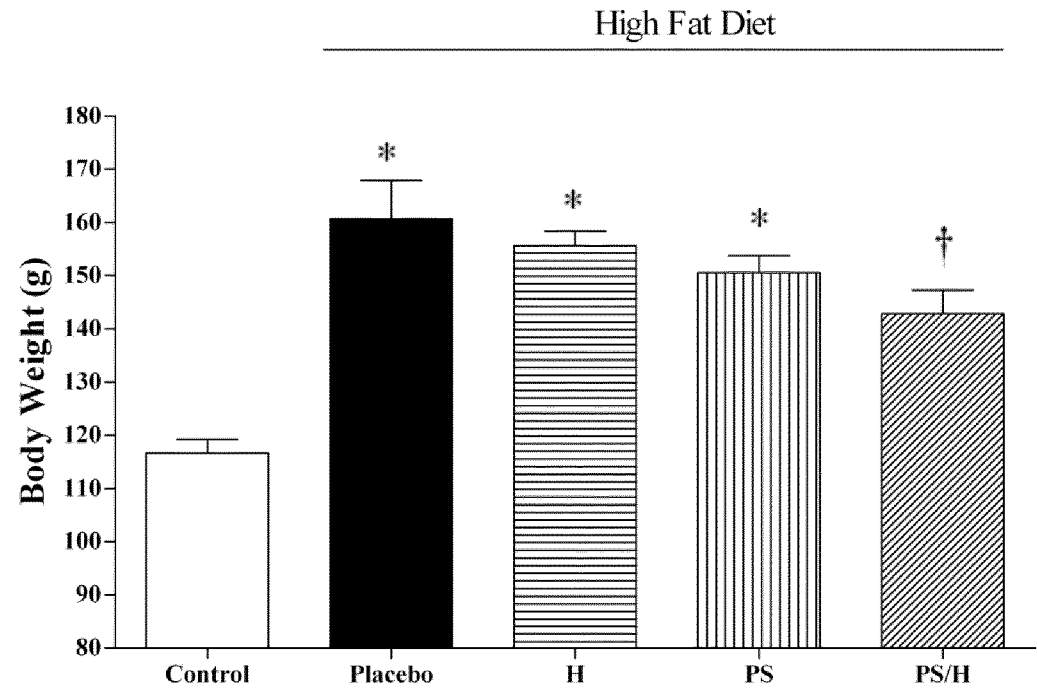


Figure 3:

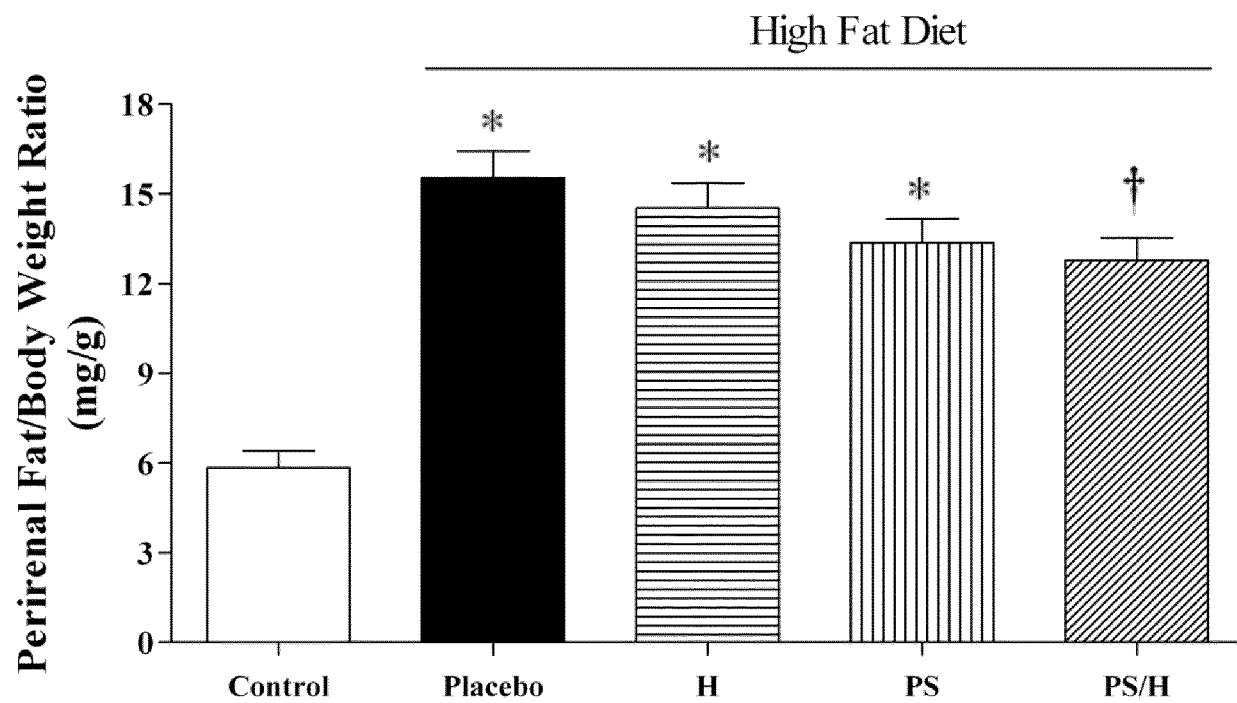
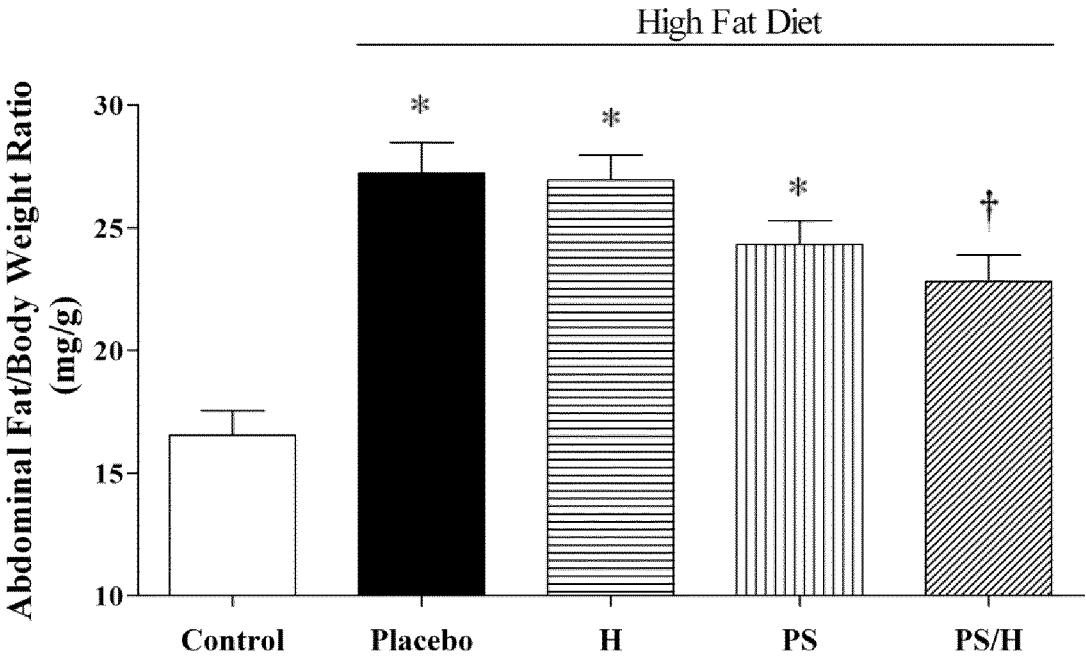


Figure 4:



INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K36/734 A61P3/04 A61P3/06 A61P3/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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)

EP0-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/039040 A1 (UNILEVER NV [NL]; UNILEVER PLC [GB]; LEVER HINDUSTAN LTD [IN]; LIN YUG) 12 April 2007 (2007-04-12) *cf. abstract, first para. at page 1, lines 18-24 at page 2, lines 8-17 at page 3, page 4, line 11 bridging with line 26 at page 5, example II at page 16ff, in context with study results exposed in page 19, lines 5-25*	1-14
X	WO 02/43506 A2 (NUTRICIA NV [NL]; CHEN QI [NL]; BONT HENDRICUS BARTHOLOMEUS AN [NL]; Z) 6 June 2002 (2002-06-06) *cf. abstract, page 5, line 24 bridging with line 7 at page 6, lines 17-24 at page 7, last para. of page 10 bridging with line 11 at page 11, further claims 1 and 5*	1-14



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

8 October 2013

Date of mailing of the international search report

21/10/2013

Name and mailing address of the ISA/

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Authorized officer

Stoltner, Anton

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/065449

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AL-HALLAQ ENTISAR K ET AL: "Evaluation of the hypocholesterolemic effect and phytochemical screening of the hydroethanolic extract of Crataegus aronia from Jordan", NATURAL PRODUCT COMMUNICATIONS, NATURAL PRODUCT INC, US, vol. 7, no. 1, 1 January 2012 (2012-01-01), pages 35-38, XP009173202, ISSN: 1934-578X *cf. summary and 3rd para. of the left-sided col. at page 37* -----	1-14
X	LIN Y ET AL: "Triterpenic acids present in hawthorn lower plasma cholesterol by inhibiting intestinal ACAT activity in hamsters", EVIDENCE-BASED COMPLEMENTARY AND ALTERNATIVE MEDICINE : ECAM, OXFORD UNIVERSITY PRESS, OXFORD, UK, 1 January 2011 (2011-01-01), pages 801272-1, XP009168806, ISSN: 1741-427X, DOI: 10.1093/ECAM/NEP007 *cf. summary and 3rd para. of the left col. at page 8* -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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