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(54) Titre : NOUVELLE UTILISATION DE PQQ ET DE SON DERIVE
(54) Title: NEW USE OF PQQ AND DERIVATIVE THEREOF

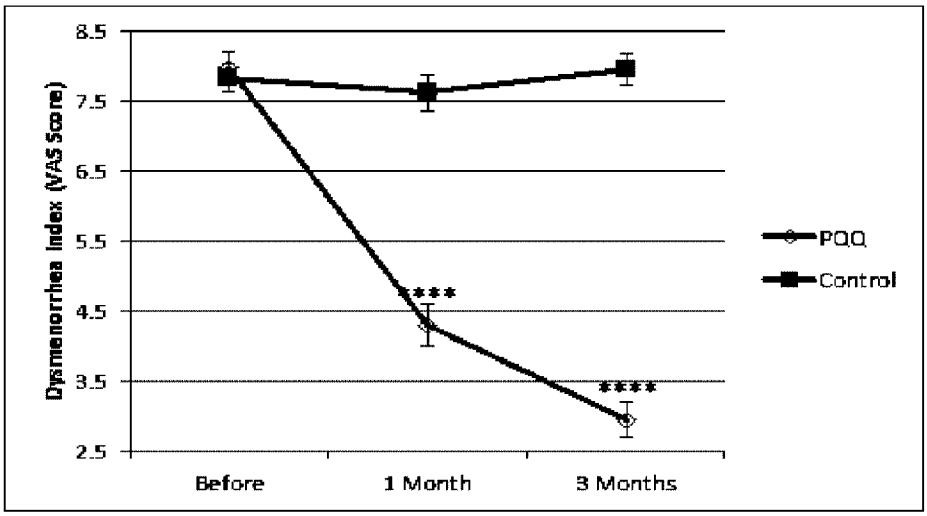

FIG. 1

(57) Abrégé/Abstract:
A new use of PQQ and a derivative thereof. PQQ can effectively alleviate or treat primary dysmenorrhea, secondary dysmenorrhea and abnormal menstruation. After being treated with PQQ, the following effects can be achieved for patients: 1. the dysmenorrhea alleviation rate is 100%; 2. the average duration of a menstrual period in each month is reduced from about 2 weeks to about 1 week, and is returned to the normal average duration of a menstrual period; 3. the menstrual blood volume in each month is reduced by more than 30% on average, and is substantially returned to the normal average level of menstrual blood volume; and 4. two patients suffering from years of infertility caused by secondary dysmenorrhea are pregnant within a treatment period of 3 months.

Date Submitted: 2023/07/18

CA App. No.: 3205533

Abstract:

A new use of PQQ and a derivative thereof. PQQ can effectively alleviate or treat primary dysmenorrhea, secondary dysmenorrhea and abnormal menstruation. After being treated with PQQ, the following effects can be achieved for patients: 1. the dysmenorrhea alleviation rate is 100%; 2. the average duration of a menstrual period in each month is reduced from about 2 weeks to about 1 week, and is returned to the normal average duration of a menstrual period; 3. the menstrual blood volume in each month is reduced by more than 30% on average, and is substantially returned to the normal average level of menstrual blood volume; and 4. two patients suffering from years of infertility caused by secondary dysmenorrhea are pregnant within a treatment period of 3 months.

NEW USE OF PQQ AND DERIVATIVE THEREOF

FIELD OF THE INVENTION

[0001] The present disclosure relates to new use of existing compounds.

BACKGROUND OF THE INVENTION

[0002] Dysmenorrhea is one of the most common gynecological symptoms, which refers to patients with lower abdominal pain, heaviness, and backache or other discomfort before and after menstruation or during menstruation, and the quality of life is seriously affected by the symptoms. Dysmenorrhea can be divided into two categories: primary dysmenorrhea and secondary dysmenorrhea. Primary dysmenorrhea refers to dysmenorrhea without organic lesions in reproductive organs; secondary dysmenorrhea refers to dysmenorrhea caused by pelvic organic diseases. The reasons of dysmenorrhea are not fully understood. It is generally believed that the pathogenesis and treatment plan of secondary dysmenorrhea are different from those of primary dysmenorrhea. Dysmenorrhea is often manifested in various ways of pain: lower abdominal pain, lower abdominal distension, pain in the anus, pain during sexual intercourse, etc.

[0003] Most mammals do not have regular menstrual cycles and mainly experience cryptomenorrhea, which is hardly comparable to the secondary menstrual pain indicators in humans. Although some primates also have menstruation, but no secondary dysmenorrhea is observed. The lack of a practical animal model available of dysmenorrhea for the development of drugs, which limits the progress of drug development. Existing papers also show that experimental results in animals or cell models of dysmenorrhea are often ineffective when applied to humans. Such as Durak, Yildirim, *et al.* ("Effect of vitamin C on the growth of experimentally induced endometriotic cysts." Journal of Obstetrics and Gynaecology Research 39.7 (2013): 1253-1258) indicated that vitamin C supplementation significantly reduced endometriotic cyst volume and weight in a dose-dependent manner. However, it is well known that vitamin C supplementation does not have any alleviating effect on human dysmenorrhea, let alone a therapeutic effect.

[0004] There are no very effective drugs for treating dysmenorrhea currently. Traditional drugs for treating dysmenorrhea mainly include hormonal drugs.

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However, treatment with hormonal or hormone-like drugs is associated with serious side effects, including but not limited to infertility, which limits its scope of application.

[0005] Pyrroloquinoline Quinone (PQQ) is a tricarboxylic acid quinone compound, CAS No. 72909-34-3, IUPAC Name: 4,5-dioxo-1H-pyrrolo[2,3-f]quinoline-2,7,9-tricarboxylic acid. PQQ is widely present in various foods. The content of PQQ in foods is about 3.65-61 ng/g, in parsley and green peppers in vegetables, kiwi and papaya in fruits, green tea and Oolong tea in drinks, tofu that people often eat, the content of PQQ is about 30ng/g. Previous studies have shown that PQQ can stimulate the speed of growth of cells of microorganisms, plants, animals and human; remove excess free radicals in body and protect body from oxidative damage; accelerate the oxidation of acetaldehyde to acetic acid to reduce the content of acetaldehyde in body, thereby it is expected to reduce the toxic damage to liver caused by alcohol consumption. *Chinese Patent Application* (*Pub. No. CN110870866A*) discloses the application of pyrroloquinoline quinone in the preparation of medicines for preventing and treating acute altitude sickness and acute altitude hypoxia injury; *Chinese Patent Application* (*Pub. No. CN110151764A*) discloses that pyrroloquinoline quinone can reduce lipopolysaccharide-induced animal fibroblasts and intestinal inflammation; *Chinese Patent Application* (*Pub. No. CN106265730A*) discloses Application of PQQ in reversing tumor multidrug resistance; *Chinese Patent Application* (*Pub. No. CN105963297A*) discloses the application of pyrroloquinoline quinone in adjuvant therapy after chemotherapy; and *Chinese Patent Application* (*Pub. No. CN103191115A*) discloses the application of pyrroloquinoline quinone in the treatment and/or alleviation of diabetic foot.

SUMMARY OF THE INVENTION

[0006] The objective of the present disclosure is to provide a new use of PQQ in the preparation of medicines for preventing and treating primary dysmenorrhea, secondary dysmenorrhea and infertility and abnormal menstruation caused by secondary dysmenorrhea.

[0007] The technical scheme adopted by the present disclosure is:

[0008] In a first aspect, the present disclosure provides:

[0009] Use of pyrroloquinoline quinone and derivatives thereof in the preparation of compositions for preventing, alleviating or treating diseases selected from:

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[0010] primary dysmenorrhea;

[0011] secondary dysmenorrhea and/or its accompanying symptoms; and

[0012] menstrual abnormalities.

[0013] In some embodiments, the accompanying symptoms of secondary dysmenorrhea are infertility caused by the treatment of secondary dysmenorrhea.

[0014] In some embodiments, said menstrual abnormalities include at least one of abnormal increase in the amount of menstrual bleeding, an abnormal increase in the duration of menstrual bleeding, and the menstrual cycle longer than 35 days.

[0015] In some embodiments, said abnormal increase in the amount of menstrual bleeding refers to the amount of menstrual bleeding is 50% greater than the amount of a healthy woman.

[0016] In some embodiments, said abnormal increase in the duration of menstrual bleeding refers to the duration of menstrual bleeding is no less than 8 days.

[0017] In some embodiments, said derivative of pyrroloquinoline quinone is a derivative digestible or metabolizable to pyrroloquinoline quinone in vivo.

[0018] In some embodiments, said derivative of pyrroloquinoline quinone is a derivative hydrolysable to pyrroloquinoline quinone in digestive tract.

[0019] In some embodiments, said derivative of pyrroloquinoline quinone is a pharmaceutical or food acceptable salt, C2-C6 ester, amide, hydrate, crystal, co-crystal or solvate.

[0020] In some embodiments, the oral dosage based on pyrroloquinoline quinone is:

[0021] about 5 mg/day to about 10 mg/day for preventing of primary dysmenorrhea or secondary dysmenorrhea;

[0022] about 15 mg/day to about 20 mg/day for alleviating or treating mild dysmenorrhea;

[0023] about 20 mg/day to about 30 mg/day for alleviating or treating moderate dysmenorrhea;

[0024] about 25 mg/day to about 100 mg/day for alleviating or treating severe dysmenorrhea;

[0025] about 20 mg/day to about 50 mg/day for alleviating or treating menstrual abnormalities.

[0026] In some embodiments, said composition is a food, a nutraceutical or a medicine.

[0027] In some embodiments, said composition further comprising pharmaceutically

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or food acceptable excipients.

[0028] In some embodiments, said excipient is selected from at least one of carriers, solvents, antioxidants, and preservatives.

[0029] In a second aspect, the present disclosure provides:

[0030] A method for preventing, alleviating or treating disease in a patient, wherein said disease is selected from:

[0031] primary dysmenorrhea;

[0032] secondary dysmenorrhea and/or its accompanying symptoms; and

[0033] menstrual abnormalities;

[0034] said method comprising:

[0035] diagnosing the patient to determine is with primary dysmenorrhea, secondary dysmenorrhea, or menstrual abnormalities;

[0036] administering (orally or by injection, etc.) to the patient a prophylactic, alleviating or therapeutic amount of at least one of pyrroloquinoline quinone or a derivative thereof.

[0037] In some embodiments, the oral dosage based on pyrroloquinoline quinone is:

[0038] about 5 mg/day to about 10 mg/day for preventing of primary dysmenorrhea or secondary dysmenorrhea;

[0039] about 15 mg/day to about 20 mg/day for alleviating or treating mild dysmenorrhea;

[0040] about 20 mg/day to about 30 mg/day for alleviating or treating moderate dysmenorrhea;

[0041] about 25 mg/day to about 100 mg/day for alleviating or treating severe dysmenorrhea; and

[0042] about 20 mg/day to about 50 mg/day for alleviating or treating menstrual abnormalities.

[0043] In some embodiments, the dosage of pyrroloquinoline quinone or derivatives thereof is adjusted according to the individual conditions, including but not limited to weight and severity of the disease of the patient.

[0044] In some embodiments, the accompanying symptoms of secondary dysmenorrhea are infertility caused by the treatment of secondary dysmenorrhea.

[0045] In some embodiments, said menstrual abnormalities include at least one of abnormal increase in the amount of menstrual bleeding, an abnormal increase in the duration of menstrual bleeding, and the menstrual cycle longer than 35 days.

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[0046] In some embodiments, at least one of the following benefits is achieved by the patient after the preventing, alleviating or treating:

[0047] pregnant able;

[0048] alleviation of dysmenorrhea, preferably the average score of menstrual dysmenorrhea pain index drops by more than 1 point or the pain level drops by one grade;

[0049] the amount of menstrual bleeding is reduced to no more than 50%, 40%, 30% of the normal menstrual bleeding of women, preferably 10%, and more preferably reduced to the normal average menstrual bleeding;

[0050] the duration of menstrual bleeding is shortened to no longer than 10 days, preferably to no longer than 9 days, 8 days, or 7 days.

[0051] The pain index or pain level is determined according to WHO standards.

[0052] In some embodiments, the accompanying symptoms of secondary dysmenorrhea are infertility caused by the treatment of secondary dysmenorrhea.

[0053] In some embodiments, said menstrual abnormalities include at least one of abnormal increase in the amount of menstrual bleeding, an abnormal increase in the duration of menstrual bleeding, and the menstrual cycle longer than 35 days.

[0054] In some embodiments, the abnormally increased amount of menstrual bleeding refers to the amount of menstrual bleeding is greater than 50% of normal menstrual bleeding of women.

[0055] In some embodiments, the abnormal increase in the duration of menstrual bleeding refers to the duration of menstrual bleeding is no less than 8 days.

[0056] In some embodiments, the derivative of pyrroloquinoline quinone is a derivative digestible or metabolizable to pyrroloquinoline quinone in vivo.

[0057] In some embodiments, the derivative of pyrroloquinoline quinone is a derivative hydrolysable to pyrroloquinoline quinone in digestive tract.

[0058] In some embodiments, the derivative of pyrroloquinoline quinone is a pharmaceutically or food acceptable salt, C2-C6 ester, amide, hydrate, crystal, co-crystal or solvate.

Beneficial effect

[0059] The inventors found PQQ is effective in preventing, alleviating or treating patient with primary dysmenorrhea, secondary dysmenorrhea and menstrual abnormalities accidentally.

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[0060] In some embodiments, after being treated with PQQ, at least one of the following effects is achieved for patients: 1. the dysmenorrhea alleviation rate is 100%; 2. the average duration of a menstrual period is reduced from about 2 weeks to about 1 week, and is returned to the normal average duration of a menstrual period; 3. the amount of menstrual blood in a menstrual period is reduced by more than 30% on average, and is substantially returned to the normal average level; and 4. two patients suffering from years of infertility caused by secondary dysmenorrhea are pregnant within a treatment period of 3 months.

BRIEF DESCRIPTION OF THE DRAWINGS

[0061] Figure 1 is the changes of the dysmenorrhea index (VAS score) in the treatment of secondary dysmenorrhea during treatment;

[0062] Figure 2 shows the changes of menstrual duration in patients with abnormal menstruation (irregular menstruation) during treatment; and

[0063] Figure 3 shows the changes in the consumption of sanitary napkins of patients with abnormal menstruation (irregular menstruation) during treatment.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0064] In present disclosure, the pharmaceutical or food acceptable derivatives of the compound refer to simple derivatives thereof, especially the lower esters, lower ethers, lower alkyl substituents, pharmaceutically acceptable salts, and lower amides which the number of carbon atoms is 1 to 6, preferably 2 to 6, and a derivative achieved by condensation of a carboxylic acid, alcohol, or amine of 2 to 4 with the parent compound. In particular, the general formula of the derivative of pyrroloquinoline quinone is as following:

[0065] In present disclosure, the pharmaceutical or food acceptable derivatives of the compound refer to simple derivatives thereof, especially the lower esters, lower ethers, lower alkyl substituents, pharmaceutically acceptable salts, and lower amides which the number of carbon atoms is 1 to 6, preferably 2 to 6, and a derivative achieved by condensation of a carboxylic acid, alcohol, or amine of 2 to 4 with the parent compound. In particular, the general formula of the derivative of pyrroloquinoline quinone is as following:

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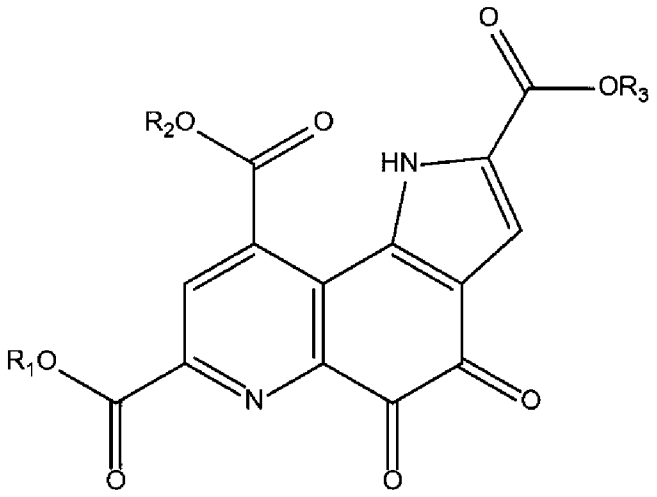

[0066] In the formula, R1 to R3 are the same or different, and are selected from H, C1 to C6 hydrocarbon groups, natural amino acid residues, Na, K, Li and other pharmaceutically acceptable groups.

[0067] Pharmaceutically acceptable salts of the compounds can be synthesized from parent compounds by conventional chemical methods, such as those in Pharmaceutical Salts: Properties, Selection, and Use, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002. In general, these salts are prepared by the reaction of the free base and acid of the compound in water or an organic solvent or a mixture of the two; Typically, non-aqueous media such as ether, ethyl acetate, ethanol, isopropanol or acetonitrile are used.

[0068] Acid addition salts can be made by various acids (inorganic and organic acids). Embodiments of acid addition salts include a salt made by a compounds reacted with an acid, said acid is selected from a group consist of acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid , L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetylamino benzoic acid, butyric acid, (+)-camphoric acid, camphor sulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, hexanoic acid, octanoic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactonic acid, gentisic acid, glucoheptonic acid, D-gluconic acid, glucuronic acid, glutamic acid , α-ketoglutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, isethionic acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, maleic acid, malic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid,

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methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxyl-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, propionic acid, L-pyroglutamic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, sulfocyanic acid, p-toluenesulfonic acid, undecylenic acid, pentanoic acid, and acylated amino acid.

[0069] In the study of PQQ, the inventors found PQQ is effective in preventing, alleviating or treating patient with primary dysmenorrhea, secondary dysmenorrhea and menstrual abnormalities accidentally.

[0070] In some embodiments, after being treated with PQQ, at least one of the following effects is achieved for patients: 1. the dysmenorrhea alleviation rate is 100%; 2. the average duration of a menstrual period is reduced from about 2 weeks to about 1 week, and is returned to the normal average duration of a menstrual period; 3. the amount of menstrual blood in a menstrual period is reduced by more than 30% on average, and is substantially returned to the normal average level; and 4. two patients suffering from years of infertility caused by secondary dysmenorrhea are pregnant within a treatment period of 3 months. Details are as following:

[0071] Treatment of patients with primary dysmenorrhea:

[0072] Experiment number: 100 people have been diagnosed with primary dysmenorrhea, 50 people in the experimental group and the control group.

[0073] Experimental method: administering PQQ orally to the patients of experimental group, administering placebo orally to the patients of control group. The duration of the experiment was 3 months, and menstrual pain was asked and recorded.

[0074] The results of the experiment:

[0075] Experimental group: the dysmenorrhea index alleviated by 100% compared to beginning of the experiment.

[0076] Control group: the dysmenorrhea index alleviated by less than 20%, compared to beginning of the experiment, and the average degree of alleviation was lower than the experimental group.

Proportion of people with alleviation in primary dysmenorrhea (self-assessment)		
Evaluation time	**PQQ group (50 people)**	**Control group (50 people)**
1 month	98%	12%
3 months	100%	16%

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[0077] Compared with the control group, the data of experimental group proved that the drug is effective with significant statistical significance for treating primary dysmenorrhea.

[0078] Treatment of patients with secondary dysmenorrhea:

[0079] Experiment number: 100 peoples have been diagnosed with secondary dysmenorrhea, with 50 peoples in the experimental group and the control group each.

[0080] Experimental method: administering PQQ orally to the patients of experimental group, administering placebo orally to the patients of control group. The duration of the experiment was 3 months, and menstrual pain and pregnancy were asked and recorded.

[0081] The results of the experiment:

[0082] Experimental group: the dysmenorrhea index alleviated by 100% compared to the beginning of the experiment; 2 cases became pregnant.

[0083] Control group: the dysmenorrhea index alleviated by less than 5% compared to the beginning of the experiment, and the average degree of alleviation was far lower than the experimental group; no case became pregnant.

Proportion of people with alleviation in secondary dysmenorrhea		
Evaluation time	**PQQ group (50 people)**	**Control group (50 people)**
1 month	82%	8%
3 months	100%	4%

[0084] Compared with the control group, the data of experimental group proved that the drug is effective with significant statistical significance for treating secondary dysmenorrhea.

[0085] The dysmenorrhea index is determined based on the VAS scoring standard, which means patients self-evaluate the intensity of pain and the degree of psychologically unpleasant experience according to the degree of pain they feel, including:

[0086] 0 points: no pain;

[0087] 1-3 points: mild pain;

[0088] 4-6 points: moderate pain;

[0089] 7-9 points: severe pain;

[0090] 10 points: unbearable pain.

[0091] The average dysmenorrhea index changes is shown in Figure 1. According to the figure, the dysmenorrhea index of the PQQ group decreased significantly, while

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the dysmenorrhea index of the control group did not change significantly. It was proved that secondary dysmenorrhea is significantly alleviating by administering PQQ preparation orally.

[0092] Treatment of patients with abnormal menstruation:

[0093] Experiment number: 100 peoples diagnosed with menstrual abnormalities, 50 people in the experimental group and the control group each.

[0094] Experimental method: administering PQQ orally to the patients of experimental group, administering placebo orally to the patients of control group. The duration of the experiment was 3 months, and menstrual conditions (duration of menstrual, consumption and weights of sanitary napkin) were measured and recorded.

[0095] The results of the experiment:

[0096] The experimental results are shown in Figure 2 and Figure 3. As shown in Figure 2 and Figure 3, in the experimental group: the menstrual duration: the average monthly menstrual bleeding duration was reduced from about 2 weeks to about 1 week compared to beginning of the experiment; the amount of menstrual bleeding: the average amount of menstrual bleeding decreased by more than 30%; in the control group: compared with the beginning of the experiment, menstrual duration: no significant alleviation; the amount of menstrual bleeding : no significant alleviation.

[0097] Compared with the control group, the data of experimental group proved that the drug is effective with significant statistical significance for treating menstrual abnormalities.

WHAT IS CLAIMED IS:

1. Use of pyrroloquinoline quinone or derivatives thereof for preparation compositions for preventing, alleviating or treating a patient with disease, wherein said disease is selected from:

primary dysmenorrhea;

secondary dysmenorrhea and/or its accompanying symptoms; and

menstrual abnormalities.

2. The use according to claim 1, wherein:

said accompanying symptom of secondary dysmenorrhea is infertility caused by secondary dysmenorrhea; and

said menstrual abnormalities include at least one of abnormal increase in the amount of menstrual bleeding, an abnormal increase in the duration of menstrual bleeding, and the menstrual cycle longer than 35 days.

3. The use according to claim 2, wherein:

said abnormal increase in the amount of menstrual bleeding refers to that the amount of menstrual bleeding is higher than 50% of the normal amount of menstrual bleeding in women; and

said abnormal increase in the duration of menstrual bleeding refers to the duration of menstrual bleeding is no less than 8 days.

4. The use according to claim 1, wherein said derivative of pyrroloquinoline quinone is a derivative digestible or metabolizable to pyrroloquinoline quinone in vivo.

5. The use according to claim 4, wherein said derivative of pyrroloquinoline quinone is a derivative hydrolysable to pyrroloquinoline quinone in digestive tract.

6. The use according to claim 4, wherein said derivative of pyrroloquinoline quinone is a pharmaceutically or food acceptable salt, C2-C6 ester, amide, hydrate, crystal, co-crystal or solvate.

7. The use according to claim 1, wherein the oral dosage based on pyrroloquinoline

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quinone is:

about 5 mg/day to about 10 mg/day for preventing of primary dysmenorrhea or secondary dysmenorrhea;

about 15 mg/day to about 20 mg/day for alleviating or treating mild dysmenorrhea;

about 20 mg/day to about 30 mg/day for alleviating or treating moderate dysmenorrhea;

about 25 mg/day to about 100 mg/day for alleviating or treating severe dysmenorrhea; and

about 20 mg/day to about 50 mg/day for alleviating or treating menstrual abnormalities.

8. The use according to claim 1, wherein said composition is a food, a nutraceutical or a medicine.

9. The use according to claim 1, wherein said composition further comprising pharmaceutical or food acceptable excipients.

10. The use according to claim 9, wherein said excipient is selected from at least one of carriers, solvents, antioxidants, and preservatives.

11. A method for preventing, alleviating or treating disease in a patient, wherein said disease is selected from:

primary dysmenorrhea;

secondary dysmenorrhea and/or its accompanying symptoms; or

menstrual abnormalities;

said method comprising:

diagnosing the patient to determine is with primary dysmenorrhea, secondary dysmenorrhea, or menstrual abnormalities;

administering to the patient a prophylactic, alleviating or therapeutic amount of at least one of pyrroloquinoline quinone or a derivative thereof;

preferably, the oral dosage based on pyrroloquinoline quinone is:

about 5 mg/day to about 10 mg/day for preventing of primary dysmenorrhea or secondary dysmenorrhea;

about 15 mg/day to about 20 mg/day for alleviating or treating mild dysmenorrhea;

about 20 mg/day to about 30 mg/day for alleviating or treating moderate dysmenorrhea;

about 25 mg/day to about 100 mg/day for alleviating or treating severe dysmenorrhea;

about 20 mg/day to about 50 mg/day for alleviating or treating menstrual abnormalities.

12. The method according to claim 11, wherein:

said accompanying symptoms of secondary dysmenorrhea are infertility caused by the treatment of secondary dysmenorrhea;

said menstrual abnormalities include at least one of abnormal increase in the amount of menstrual bleeding, an abnormal increase in the duration of menstrual bleeding, and the menstrual cycle longer than 35 days.

13. The method according to claim 11, wherein at least one of the following benefits is achieved by the patient after the preventing, alleviating or treating:

1) pregnant able;

2) alleviation of dysmenorrhea, preferably the average score of menstrual dysmenorrhea pain index drops by more than 1 point or the pain level drops by one grade;

3) the amount of menstrual bleeding is reduced to no more than 50%, 40%, 30% of the normal menstrual bleeding of women, preferably 10%, and more preferably the normal average bleeding;

said duration of menstrual bleeding is shortened to no longer than 10 days, preferably to no longer than 9 days, 8 days, or 7 days.

14. The method according to claim 11, wherein said derivative of pyrroloquinoline quinone is a derivative digestible or metabolizable to pyrroloquinoline quinone in vivo.

15. The method according to claim 14, wherein said derivative of pyrroloquinoline quinone is a derivative hydrolysable to pyrroloquinoline quinone in digestive tract.

16. The method according to claim 14, wherein said derivative of pyrroloquinoline quinone is a pharmaceutical or food acceptable salt, C2-C6 ester, amide, hydrate, crystal,

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co-crystal or solvate.

17. The method according to claim 11, wherein the frequency of administering pyrroloquinoline quinone or derivative thereof is once a day.

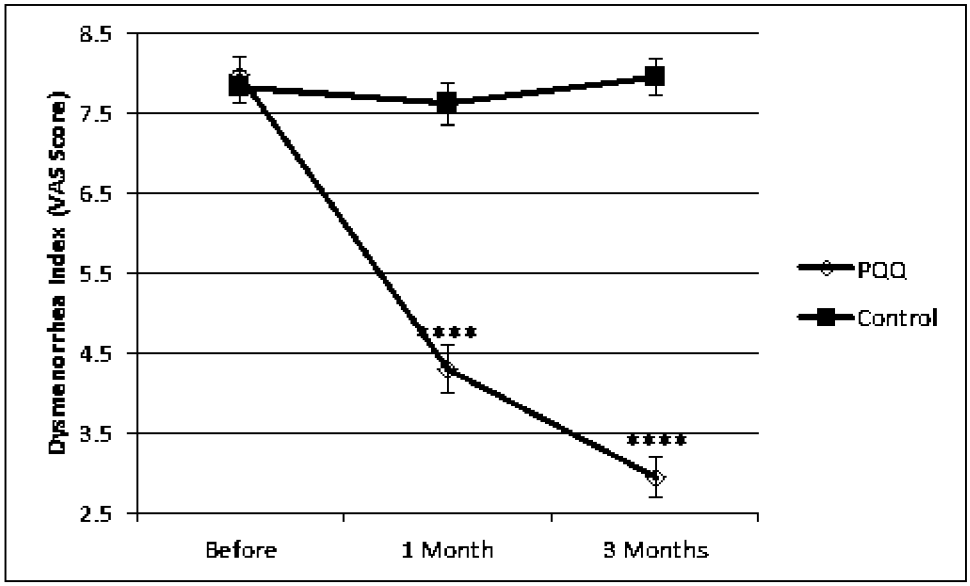
8.5
7.5
6.5
5.5
4.5
3.5
2.5
Dysmenorrhea Index (VAS Score)
****
****
Before
1 Month
3 Months
PQQ
Control

FIG. 1

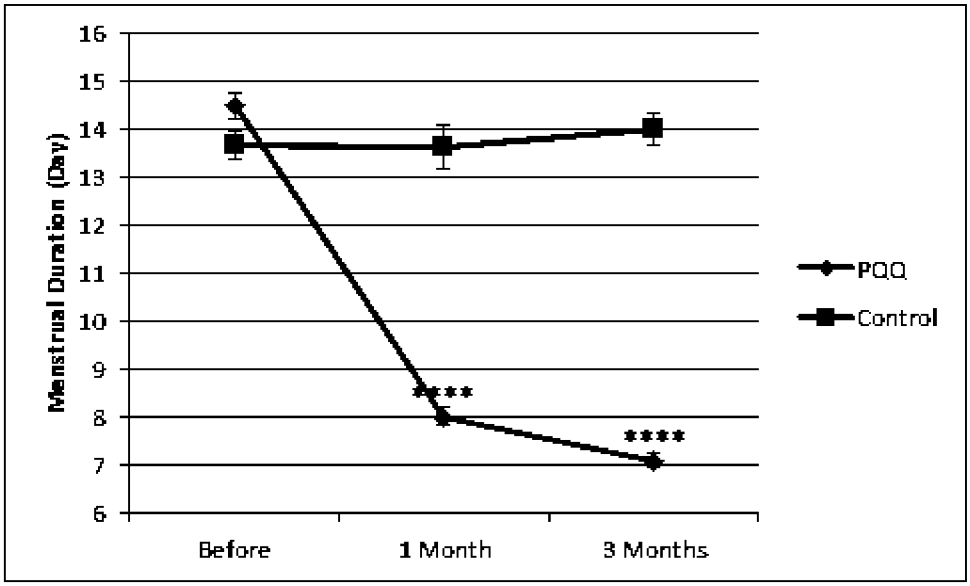
16
15
14
13
12
11
10
9
8
7
6
Menstrual Duration (Day)
****
****
Before
1 Month
3 Months
PQQ
Control

FIG. 2

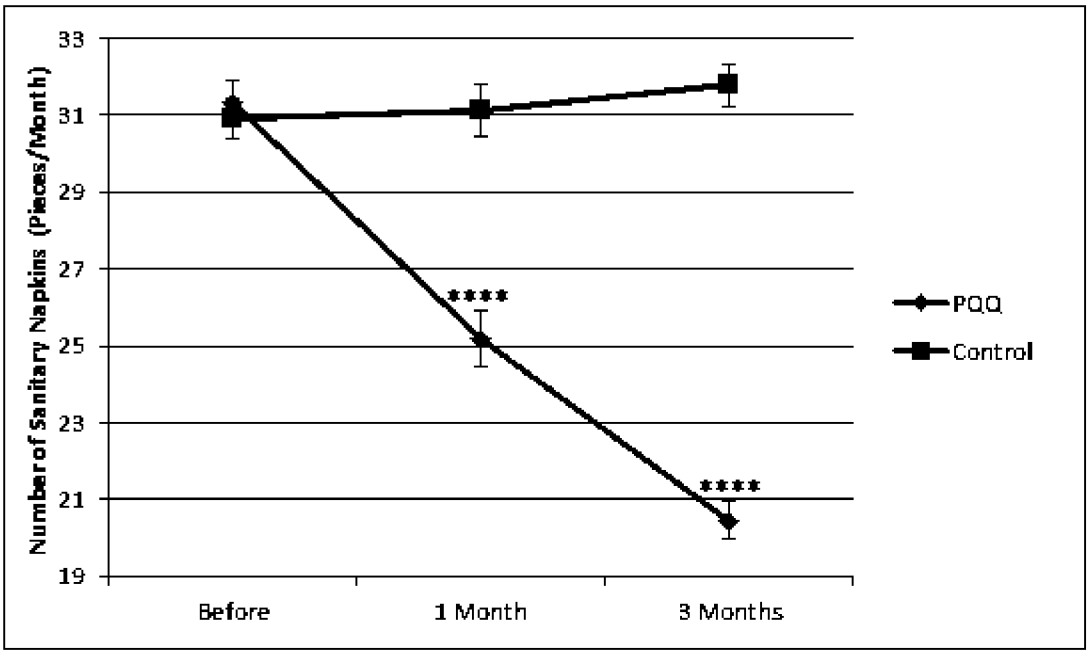
33
31
29
27
25
23
21
19
Number of Sanitary Napkins (Pieces/Month)
****
****
Before
1 Month
3 Months
PQQ
Control

FIG. 3