Title: METHODS FOR IMPROVING FEMALE SEXUAL FUNCTION

Abstract: Methods and pharmaceutical formulations for treating female sexual dysfunction are disclosed. In particular, compositions are disclosed of L-arginine or a precursor thereof and a proanthocyanidins containing extract for oral administration. The compositions are useful for improving female sexual function.
METHODS FOR IMPROVING FEMALE SEXUAL FUNCTION

RELATED APPLICATIONS

This application claims the benefit of priority to US application 61/000,242 filed October 23, 2007, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to methods and pharmaceutical formulations for improving female sexual function.

BACKGROUND OF THE INVENTION

Sexual response in women is generally classified into four stages: excitement, plateau, orgasm, and resolution. Masters and Johnson, Human Sexual Response (Little, Brown & Co., Boston, Mass. 1966). With sexual arousal and excitement, vasocongestion and muscular tension increase progressively, primarily in the genitals, and is manifested by increased blood flow, elevated luminal oxygen tension, and vaginal surface lubrication as a result of plasma transudation that saturates the fluid reabsorptive capacity of the vaginal epithelium.

Sexual excitement is initiated by any of a number of psychogenic or somatogenic stimuli and must be reinforced to result in orgasm. With continued stimulation, excitement progresses in intensity into a plateau stage, from which the individual can shift into orgasm. The orgasmic stage is characterized by a rapid release from vasocongestion and muscular tension. During the various stages of sexual response, characteristic genital and extragenital responses occur.

Female sexual dysfunction can be divided into four often overlapping categories:

- **Low sexual desire** - characterized by poor libido or lack of sex drive;
- **Sexual arousal disorder** - characterized by an inability to become aroused or to maintain arousal during sexual activity, even though sexual desire may be intact;
- **Orgasmic disorder** - characterized by an inability to achieve orgasm after sufficient sexual arousal and stimulation; and
- **Sexual pain disorder** - characterized by pain associated with sexual stimulation or vaginal contact.
Sexual dysfunction may be due to organic or functional disturbances. For example vaginal atrophy and dyspareunia are common causes of sexual dysfunction. During vaginal atrophy, the vaginal epithelium decreases in thickness, hydration, rugae (folds), and blood flow. For a discussion of other causes of female sexual dysfunction, see, e.g., Kaplan, The Evaluation of Sexual Disorders: Psychological and Medical Aspects (Brunner-Mazel, New York, N.Y. 1983), and Kolodny et al, Textbook of Sexual Medicine (Little, Brown & Co., Boston, Mass. 1979).

Furthermore, excitement stage dysfunction generally involves touch sensation impairment, loss of clitoral sensation, vaginal dryness, and urinary incontinence. Such excitement phase dysfunction generally results in dyspareunia. Dyspareunia is thought to affect approximately 40% of women, due in large part to inadequate lubrication. Contemporary symptomatic treatments generally involve the use of physiologically safe personal lubricants, such as K-Y® Jelly, Replens® and Astroglide®. However, these products provide only temporary symptomatic relief and provide virtually no long-term benefits to the vaginal tissue. When symptomatic treatment fails, pharmacological treatment may be indicated.

Estrogen therapy is commonly used in the pharmacological treatment of female sexual dysfunction. Estrogen-based therapies are generally used to increase mucous production, provide vasodilatory effects, or to increase the general health of the vagina. In such treatments, estrogen is administered orally, parenterally (e.g., by injection), or topically. However, estrogen-based therapies are known to increase the risk of endometrial hyperplasia, endometrial cancer and breast cancer in treated individuals.

Because of the increased risk of various types of cancer associated with estrogen therapies, estrogen/progestogen combinations have been employed. However, progestogens are known to have some androgenic activity. Further, common side effects from such therapies include uterine bleeding and the continuation of menstrual periods. Accordingly, as female sexual dysfunction creates a variety of quality of life issues for women and their partners, there remains a need in the art to provide safe compositions and methods for treating female sexual dysfunction.

Monitoring Female Sexual Function and/or Dysfunction:

It is known that during normal sexual function, the female undergoes many physiological changes. These changes include, among others, increased labial flow, dilation of the introitus, changes in vaginal-wall blood flow (resulting in color change, for example), vaginal lubrication (transudates), vaginal dilation, vaginal lengthening, nipple
and clitoral erections, muscle contractions, pupil dilation, increased blood pressure and heart rate, and skin blushing. These changes may be monitored to determine the extent of female sexual dysfunction and recovery from dysfunction.

Methods of monitoring female sexual function and dysfunction are known. Devices and methods for measuring physiological changes, including changes during sexual arousal, which occur in the female are known. The changes that can be measured include changes in clitoral, vaginal-artery, and/or vaginal-capillary blood flow, clitoral engorgement, and bioimpedance. Overnight arousal-event monitoring, or other continuous monitoring methods over extended periods of time are also known. These devices and methods, some of which are patented, provide objective, quantifiable measures of multiple physiological variables associated with female arousal.

It is known that Doppler velocimetry may be used to measure vaginal blood flow in human subjects. One of the physiological changes that occurs during female sexual arousal is an increase in vaginal-wall blood flow. Vaginal wall capillary blood flow changes have been measured by photoplethysmography. Other methods of monitoring female sexual function including changes in clitoral, vaginal-artery, and/or vaginal-capillary blood flow, clitoral engorgement, and bioimpedance, and contrast enhanced imaging of sexual response are known and discussed in one or more of the following U.S. Patents: US5,782,778, US6,169,914, US6,969,507.

**SUMMARY OF THE INVENTION**

In one aspect, a method of improving a female sexual response is provided that includes administering to a patient with a reduced female sexual response an effective amount of a composition comprising a NO precursor and a vaginal blood flow enhancing agent, thereby enhancing at least one sexual response characteristic selected from the group consisting of: (1) vaginal blood flow; (2) vaginal blood volume; (3) vaginal mucosal flux; (4) vaginal mucosal thickness; (5) clitoral sensitivity; and (6) combinations of the foregoing.

In another aspect, a method of treating female sexual arousal inadequacy is provided that includes administering to a patient with at least one symptom of female sexual arousal inadequacy an effective amount of a composition comprising a NO precursor and a vaginal blood flow enhancing agent, thereby improving at least one vaginal sexual response characteristic. In this method, the at least one symptom of female sexual arousal inadequacy can be selected from the group consisting of (a) inadequate
vaginal blood flow; (b) inadequate vaginal blood volume; (c) inadequate vaginal mucosal
flux; (d) inadequate vaginal mucosal thickness; (e) inadequate clitoral sensitivity; (f)
decreased autonomic sexual function; (g) age-related atrophy of neurons innervating the
clitoris; and (h) combinations of the foregoing.

While any period of administration is contemplated for the foregoing methods,
Applicants find that continued administration for a period of at least 4 weeks or at least 8
weeks to be particularly effective.

The one or more vaginal sexual response characteristics which is to be improved,
for methods of this invention, is selected from the group consisting of: (1) vaginal blood
flow; (2) vaginal blood volume; (3) vaginal mucosal flux; (4) vaginal mucosal thickness;
(5) clitorial sensitivity; and (6) combination of the foregoing. In some embodiments,
these vaginal sexual response characteristics can be improved during sexual arousal.

For any of the methods of this invention, the NO precursor can comprise L-
arginine. In some embodiments, the NO precursor is L-arginine or salts of L-arginine. In
some embodiments, the NO precursor is arginine aspartate.

The vaginal blood flow enhancing agent, for any of the methods of this invention,
can be a proanthocyanidins containing extract. In some embodiments, the
proanthocyanidins containing extract is a pine bark extract. The pine bark extract can
contain at least 50% proanthocyanidins.

The agent can function by enhancing nitric oxide synthesis in the brain or in the
genitals of a female recipient/patient and thereby (1) ameliorate a female sexual arousal
disorder, (2) ameliorate a female orgasmic disorder, (3) ameliorate a female sexual pain
disorder, or (4) increase sexual desire in the female.

For the methods of this invention, the proanthocyanidins containing vaginal blood
flow enhancing agent further comprises a nitric oxide synthase enhancing activity. Since
one agent contains both vaginal blood flow enhancing activity and nitric oxide synthase
enhancing activity, these two activities are linked.

The compositions administered in the foregoing methods can involve a dosage of
between 40 mg/day to 160 mg/day of proanthocyanidins extract and between 1.5 g/day to
6 g/day of L-arginine. In preferred embodiments, the dosage is about 80 mg/day of
proanthocyanidins and about 3 g per day of L-arginine.

In some embodiments of the foregoing methods, the females are diabetic females.

It is contemplated that whenever appropriate, any embodiment of the present
invention can be combined with one or more other embodiments of the present invention,
even though the embodiments are described under different aspects of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

It is understood that the term "pine bark extract" in this disclosure refers to a French maritime pine bark extract which is, for example, commercially available as Pycnogenol® (Horphag). It is also understood that a pine bark extract is one form of a proanthocyanidins containing extract. The terms "Pycnogenol ®", "pine bark extract" and "French maritime pine bark extract" are interchangeable in this disclosure.

*Pinus pinaster* (P. pinaster) and *Pinus maritima* (P. maritime), are understood to refer to the same organism. Hence, these terms are interchangeable.

Proanthocyanidins designate a group of flavonoids that includes the subgroups procyanidins, prodelphinidins and propelargonidins. Proanthocyanidins are homogeneous or heterogeneous polymers consisting of the monomer units catechin or epicatechin, which are connected either by 4-8 or 4-6 linkages, to the effect that a great number of isomer proanthocyanidins exist. Typically, the proanthocyanidins oligomers have a chain length of 2-12 monomer units. Proanthocyanidins may be synthesized or extracted from a plant material. Proanthocyanidins are extracted from plant material by conventional methods using solvents like water, ethanol or acetone or fluid carbon dioxide. The extracts are purified by solvent/solvent extraction, ultra filtration or chromatographic procedures. The purified extracts are concentrated by solvent evaporation, freeze drying or spray drying. Nonlimiting examples of plant material sources of proanthocyanidins include grape seeds, grape skin, pine barks, ginkgo leaves, peanuts, cocoa beans, tamarind, tomato, almond, apple, cranberry, blueberry, and tea leaves.

A well-known product containing proanthocyanidins, which is available in trade as a preparation of a food supplement under the name Pycnogenol®, is an extract of the maritime pine bark (*Pinus pinaster*). Pycnogenol®, the extract from French maritime pine bark (*Pinus pinaster*) is a registered trademark belonging to Horphag Research, Ltd. Pycnogenol® is a standardized bark extract of the French maritime pine *Pinus pinaster, Aiton, subspecies Atlantica des Villar* (Pycnogenol®, Horphag Research Ltd., UK). The quality of this extract is specified in the United States Pharmacopeia (USP 28)(Maritime Pine Extract. In: United States Pharmacopeia. Rockville: United States Pharmacopeial Convention, Inc.; 2005. pp. 2115-2116.). Between 65-75% of Pycnogenol® are
procyanidins comprising catechin and epicatechin subunits with varying chain lengths (Rohdewald P. A review of the French maritime pine bark extract (Pycnogenol), an herbal medication with a diverse clinical pharmacology (Int J Clin Pharmacol Ther 2002;40: 158-168.). Other constituents are polyphenolic monomers, phenolic or cinnamic acids and their glycosides (Id).

The term "extract", as used herein includes any preparation obtained from plants, fruits or vegetables using an extraction method.

By an "effective" amount or a "therapeutically effective amount" of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect, e.g., treatment of female sexual dysfunction. An appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, and improvement or remediation of damage. Thus, for example, "treating" sexual dysfunction, as the term is used herein, encompasses both prevention of sexual dysfunction in a clinically asymptomatic individual and treatment of dysfunction in a clinically symptomatic individual.

By "enhancing a female sexual response" or "treating female sexual arousal inadequacy" is meant enhancing female sexual desire and responsiveness; and optionally, to increase nitric oxide activity in the brain and in the genitals. Applicants intend to include the treatment of disorders of female sexual desire and/or response, meaning any disorder or dysfunction that causes a decrease in or absence of female sexual responsiveness or female sexual desire. This includes any persistent or recurrent deficiency in the desire for sexual activity. It also includes decreases in the physiological response to sexual stimulation such as slowed or decreased erectile response of the female erectile tissues; slowed, decreased or absent lubrication of the vagina; slowed, decreased, or absent ability to have orgasms; decreased intensity of or pleasure in orgasms; frigidity; sexual aversion; and disorders of female sexual desire and response that are secondary to a general medical condition such as the menopausal or post-menopausal state, radiotherapy of the pelvis, atherosclerosis, pelvic trauma or surgery, peripheral neuropathies, autonomic neuropathies, diabetes mellitus, and disorders of the innervation of any of the sexual organs. This term also includes substance-induced sexual
dysfunction, including but not limited to, decreases in desire and responsiveness secondary to anti-depressants, neuroleptics, anti-hypertensives, tobacco, opiates, alcohol and any other drug found to decrease or eliminate any part of the sexual response cycle.

It will be appreciated by those skilled in the art that various omissions, additions and modifications may be made to the invention described above without departing from the scope of the invention, and all such modifications and changes are intended to fall within the scope of the invention, as defined by the appended claims. All references, patents, patent applications and other documents cited are herein incorporated by reference in their entireties.

EXAMPLE 1

Evaluation of Intravital Vaginal Mucosal Flux in Menopausal and Pre-Menopausal Women

MUCOSAL FLUX (measured with laser Doppler flowmetry) is altered in most pre- or menopausal women as well as in women in the post-menopausal period. Basically, an alteration in flux is characterized by: (a) a decrease in basic mucosal flux; (b) a decrease in vasomotor variations (i.e. those due to changes in position, from supine to standing or to respiratory variations in flux); (c) a decrease in oxygen levels, (d) a general increase in dryness of the mucosa is associated with these microcirculatory changes.

These microcirculatory changes are associated with a number of signs/symptoms (linked mainly to mucosal dryness which may alter the sexual life and its quality in many women) which, apparently evolve in connection with a progressive decrease in mucosal perfusion and its increase in dryness in a process of slow atrophy which may lead to complex sexual problems. Most of these changes appear to be associated to hormonal changes during the menopausal period.

To determine if the administration of a combination of proanthocyanidins and L-arginine can overcome these symptoms, a study was performed on a number of subjects. Inclusion criteria: patients were included in the study if they exhibited one of more of the following symptoms: (1) low vaginal blood flow before or during arousal; (2) vaginal blood volume before or during arousal; (3) vaginal mucosal flux before or during arousal; (4) vaginal mucosal thickness before or during arousal; or (5) clitoral sensitivity before or during arousal.
Specifically, vaginal blood flow, vaginal blood volume and vaginal mucosal flux can be measured by noninvasive laser Doppler mucosal flow/flux measurements. Vaginal mucosal thickness may be measured by rheometer or viscometer apparatus for measuring such viscoelastic properties (L. E. Kopita and HJ. Kosasky, "The tackiness rheometer determination of the viscoelasticity of cervical mucus", Human Ovulation, edited by E.S.E. Hafez, Elsevier, North-Holland Biomedical Press, 1979. See, also, U.S. Pat. Nos. 4,002,056; and 4,779,627). Clitoral sensitivity was measured by patient survey.

Patients were determined to suffer from one or more of the above symptoms by analysis by noninvasive laser Doppler mucosal flow/flux measurements. After analysis, administration of a combination of proanthocyanidins and L-arginine was given to each patient in the study. The dosage given was 80 mg/day of proanthocyanidins (in the form of Pycnogenol®) and 3 g/day of L-arginine.

After 4 weeks of administration, patients were measured again. It was found that the administration of the composition improved perfusion at the external and internal mucosal areas. In 13 pre-menopausal women, the relative flux increase was measured at 24%-129% of the inclusion value - that is, the measured relative flux was between 124% or 229% of the inclusion value. In the same experiment, the post menopausal women showed in increase of relative flux of 53% to 239% - that is, the measured relative flux was between 153% or 339% of the measured inclusion value. In both premenopausal and menopausal groups, vasomotion was improved. Increased mucosal thickness and increased mucosal hydration was observed by ultrasound. Dryness was reduced substantially for both premenopausal and menopausal women.

The optimum dosage for this treatment is between 40 to 160 mg/day of Pycnogenol® and 1.5 to 6 grams/day of L-arginine per patient. A preferred dosage would be about 80 mg Pycnogenol® and 3 grams of L-arginine per female per day. At this dosage, the symptoms of vaginal blood flow; vaginal blood volume; vaginal mucosal flux; vaginal mucosal thickness; and clitoral sensitivity are at a combined maximum.

Surprisingly, in a subgroup of diabetic women undergoing the study, the improvements were more substantial than the non-diabetic group indicating improved responsiveness to the treatment regimen that is two fold, four fold or up to eight fold more effective than that of a non-diabetic patient.
CLAIMS

What is claimed is:

1. A method of improving a female sexual response, comprising:
   administering to a patient with a reduced female sexual response an effective amount of a composition comprising a NO precursor and a vaginal blood flow enhancing agent, thereby enhancing at least one vaginal sexual response characteristic, wherein at least one vaginal sexual response characteristic is selected from the group consisting of:
   - vaginal blood flow;
   - vaginal blood volume;
   - vaginal mucosal flux;
   - vaginal mucosal thickness;
   - clitoral sensitivity; and
   - a combination thereof.

2. The method of claim 1 wherein the at least one vaginal sexual response characteristic is enhanced during sexual arousal.

3. The method of claim 1 wherein said NO precursor comprises L-arginine.

4. The method of claim 3 wherein said NO precursor is L-arginine or salts thereof.

5. The method of claim 3 wherein said NO precursor is arginine aspartate.

6. The method of claim 1 wherein said vaginal blood flow enhancing agent is a proanthocyanidins containing extract.

7. The method of claim 6 wherein said proanthocyanidins containing extract is a pine bark extract.

8. The method of claim 7 wherein said pine bark extract contains at least 50% proanthocyanidins.

9. The method of claim 1 wherein said vaginal blood flow enhancing agent enhances nitric oxide synthesis in the brain or in the genitals of said female and thereby ameliorates a female sexual arousal disorder, ameliorates a female orgasmic
disorder, ameliorates a female sexual pain disorder or increases sexual desire in said female.

10. The method of claim 6 wherein said proanthocyanidins containing agent further comprises a nitric oxide synthase enhancing activity whereby said vaginal blood flow enhancing activity and said nitric oxide synthase enhancing activity are linked because they are provided by the same agent.

11. The method of claim 1 wherein said female is a diabetic female.

12. The method of claim 1 wherein the composition is administered for a period of not less than 4 weeks.

13. The method of claim 1 wherein the composition is administered at a dose of between 40 mg/day to 160 mg/day of proanthocyanidins extract and between 1.5 g to 6 g/day of L-arginine.

14. A method of treating female sexual arousal inadequacy, comprising: administering to a patient with at least one symptom of female sexual arousal inadequacy an effective amount of a composition comprising a NO precursor and a vaginal blood flow enhancing agent, thereby improving at least one vaginal sexual response characteristic.

15. The method of claim 14 wherein said at least one symptom of female sexual arousal inadequacy is selected from the group consisting of:

   inadequate vaginal blood flow;
   inadequate vaginal blood volume;
   inadequate vaginal mucosal flux;
   inadequate vaginal mucosal thickness;
   inadequate clitoral sensitivity; and
   a combination thereof.

16. The method of claim 14 wherein said NO precursor comprises L-arginine.

17. The method of claim 16 wherein said NO precursor is L-arginine or salts thereof.

18. The method of claim 16 wherein said NO precursor is arginine aspartate.
19. The method of claim 14 wherein said vaginal blood flow enhancing agent is a 
proanthocyanidins containing extract.

20. The method of claim 19 wherein said proanthocyanidins containing extract is a 
pine bark extract.

21. The method of claim 20 wherein said pine bark extract contains at least 50% 
proanthocyanidins.

22. The method of claim 14 wherein said vaginal blood flow enhancing agent 
enhances nitric oxide synthesis in the brain or in the genitals of said female and 
thereby ameliorates a female sexual arousal disorder.

23. The method of claim 19 wherein said proanthocyanidins containing agent further 
comprises a nitric oxide synthase enhancing activity whereby said vaginal blood 
flow enhancing activity and said nitric oxide synthase enhancing activity are 
linked because they are provided by the same agent.

24. The method of claim 14 wherein said female sexual arousal inadequacy comprises 
a symptom selected from the group consisting of:
decreased autonomic sexual function
age-related atrophy of neurons innervating the clitoris; and
a combination thereof.

25. The method of claim 14 wherein the female is a diabetic female.

26. The method of claim 14 wherein the composition is administered for a period of 
not less than 4 weeks.

27. The method of claim 14 wherein the composition is administered at a dose of 
between 40 mg/day to 160 mg/day of proanthocyanidins extract and between 1.5 g 
to 6 g/day of L-arginine.
**INTERNATIONAL SEARCH REPORT**

**Form PCT/ISA/21 0 (second sheet) (April 2005)**

**A. CLASSIFICATION OF SUBJECT MATTER**
INV. A61K31/198 A61K36/15 A61P15/02 A61P15/12

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 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 practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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Further documents are listed in the continuation of Box C

See patent family annex

* Special categories of cited documents

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on novelty claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search
3 February 2009

Date of mailing of the international search report
17/02/2009

Name and mailing address of the ISA
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Fax (+31-70) 340-3016

Authorized officer
Böttner, Ulf
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Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

1. Claims Nos 1-27 because claims 1-27 are directed to a method of treatment of the human/animal body. The search has been earned out and based on the alleged effects of the compound/composition.

2. Claims Nos because they relate to subject matter not required to be searched by the Authority, namely:

3. Claims Nos because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 64(a).

Observations where unity of Invention is lacking (Continuation of item 3 of first sheet)

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims. It is covered by claims Nos.

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of protest fee.
- The additional search fees were accompanied by the applicants' protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.
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