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(54) Title: CONTRACEPTIVE USE OF TRITERPENOIDS

(57) Abstract: Disclosed are systemic and intravaginal non-hormonal contraceptives comprising a spermicidal triterpenoid. The contraceptive may be in the form of a foam, cream or gel, or in unit form of a pill, vaginal contraceptive film (VCF), suppository, sponge, transdermal or hypodermal patches or a slow release intravaginal device or intrauterine device such as a drug-impregnated silicone elastomer vaginal ring or polymeric IUD.

Contraceptive Use of Triterpenoids

Inventors: Polina V. Lishko, Nadja Mannowetz, all of University of California, Berkeley, CA
Applicant/Assignee: The Regents of the University of California
Priority: This application claims priority to US Ser No. 62/442,964; filed: Jan 05, 2017

This invention was made with government support under Grant Numbers R01GM111802 and R21HD081403 awarded by the National Institutes of Health. The government has certain rights in the invention.

[001] Introduction

[002] In order to succeed in fertilization event, mammalian sperm must penetrate the egg protective shields. This is achieved by sperm enhanced motility mode: the specific drilling motion that is called hyperactivation. The female sex hormone progesterone (P4) that is released from the ovulated egg triggers sperm hyperactivation by activating the calcium influx into sperm tail via the calcium channel of sperm CatSper (1-5) The two steroid hormones progesterone and pregnenolone sulfate (PregS) activate CatSper via a specific signaling mechanism by binding to their receptor on the sperm tail- the enzyme α/β hydrolase domain–containing protein 2 (ABHD2). This means that sperm activation and thus fertilization are dependent on the presence of certain steroid hormones.

[003] As spermatozoa travel through the male and female reproductive tract, they are exposed to a variety of steroid hormones, such as testosterone and estrogen. Rising levels of the steroid hormone cortisol in the body as a result of stress are known to impact fertility (6) by interfering with spermatogenesis and/or sperm functions. Recently, we showed that testosterone, estrogen and cortisol impair CatSper activation by competing with progesterone (7). This indicates that compounds structurally related to the mentioned above steroids may function in the same way by preventing sperm activation. Structurally related to steroid hormones are plant triterpenoids that have been shown to exhibit antifertility properties in mice and rats. The most extensively studied plant triterpenoid with regard to male fertility is lupeol, which is found in mangoes, grapes and olives. It has been shown to possess antifertility properties when orally administered to rats (8). Another plant triterpenoid, pristimerin, which is found in *Tripterygium wilfordii* (also known as "Thunder God Vine") and *Celastrus regelii*, acts as a monoacylglycerol lipase inhibitor, a class of enzymes to which the sperm progesterone receptor ABHD2 belongs. It inhibits the hydrolysis of 2-arachidonoylglyceol (2-AG) to arachidonic acid (AA) and glycerol (9). In sperm 2-AG acts as an endogenous CatSper inhibitor and 2-AG degradation is mediated

byABHD2 in a P4-dependent manner (3). We hypothesized that pristimerin and lupeol can interfere with ABHD2 activity, and explored the ability of these triterpenoids to prevent CatSper activation and thus fertilization.

[004] Summary of the Invention

[005] The invention provides methods, systems and devices for delivering non-hormonal contraceptive active compounds that comprise naturally occurring and purified or chemically derived terpenoids, as for example an intravaginal contraceptive, orally administrable contraceptive formulation, such as a pill, or an injectable or transdermal contraceptive formulation, particulary in unit dosage and comprising a spermicidal triterpenoid.

[006] Suitable, active terpenoids (e.g. triterpenoids) are readily selected by those skilled in the art according to the disclosed sperm assays, and may be selected or derived from numerous natural, synthetic and engineered sources (10-13).

[007] In embodiments:

[008] – the contraceptive is in the form of a pill, patch, microneedle or intravaginal form such as film, foam, cream, or gel, particularly in a predetermined, unit dosage effective for contraception;

[009] - the contraceptive is in unit form of a vaginal contraceptive film (VCF), suppository, sponge, or slow release intravaginal devices or intrauterine devices such as drug-impregnated silicone elastomer vaginal rings or polymeric IUDs, and the terpenoid (e.g. triterpenoid) is in a predetermined, unit dosage effective for contraception;

[010] – the terpenoid (e.g. triterpenoid) inhibits human sperm hyperactivation induced by either progesterone (P4), pregnenolone sulfate (PregS), or fallopian tube factorinduced activation of the principal human sperm calcium channel, CatSper, such as indicated by influx of calcium currents ($I_{CatSper)}$ through the channel measured by electrophysiology and/or calcium imaging;

[011] - the terpenoid (e.g. triterpenoid) inhibits P4-, PregS, or fallopian tube factor-induced human sperm hyperactivation or motility;

[012] - the triterpenoid is at least one of: a plant triterpenoid, a pentacyclic triterpenoid, a triterpenoid quinone methide or an 11-unsubstituted (11-H) triterpenoid; in particular, we found that position 11-modifications can be detrimental for activity; consistently, RU-486 (mifepristione), and progesterone-11-biotin and progesterone-11-BSA- and all were inactive, whereas progesterone-3-biotin and progesterone -3-BSA were as active as progesterone;

[013] - the triterpenoid comprises the ring structure of pristimerin or lupeol, or is a derivative thereof, such as celastrol.

[014] - the triterpenoid is selected from pristimerin and lupeol.

[015] In another aspect, the invention provides methods of making and using the subject contraceptives, such as by manufacturing the triterprenoid in a disclosed form, and/or delivering the contraceptive to a vagina, or via the oral delivery route.

[016] In another aspect the invention provides a method of inhibiting sperm motility comprising contacting the sperm with an effective amount of a subject spermicidal triterpenoid, such as in a subject form.

[017] The invention provides reagents and kits for practicing the disclosed methods.

[018] The invention encompasses all combinations of the particular embodiments recited herein, as if each combination had been laboriously recited, such as wherein the triterpenoid is pristimerin or lupeol and the form is a pill, a microneedle, a slow release intravaginal device or intrauterine device such as a drug-impregnated silicone elastomer vaginal ring or polymeric IUD, and the triterpenoid is in a predetermined, unit dosage effective for contraception.

[019] Description of Particular Embodiments and Delivery Methods of the Invention

[020] Unless contraindicated or noted otherwise, in these descriptions and throughout this specification, the terms "a" and "an" mean one or more, the term "or" means and/or and polynucleotide sequences are understood to encompass opposite strands as well as alternative backbones described herein.

[021] The examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein, including citations therein, are hereby incorporated by reference in their entirety for all purposes.

[022] Embodiments to deliver active agent(s) include but are not limited to vaginal rings, pills and transdermal patches that release the active agent(s) at a predefined rate.

[023] In embodiments:

[024] - the delivery method is in the form of a vaginal ring: A vaginal ring may be a flexible device measuring 20-80 mm in diameter and 2-10 mm in thickness. The ring may consist of poly(ethylene-co-vinyl acetate), ethylene vinyl acetate copolymer, or silicone elastomer that contains crystals of either pristimerin, lupeol or both. This ring contains sufficient amount of active compound(s) to maintain stable blood concentrations for about 5 weeks releasing between 1 and 100 mcg of active compound(s)/24 hours, but is intended to be used for 3 weeks followed by a ring-free week.

[025] – the delivery method is in the form of a pill: The pill may contain sufficient

concentrations of active compound(s) (e.g. pristimerin, lupeolor both) to maintain stable blood concentrations by releasing between 1 to 100 mcg of active compound(s)/24hours. The pill may be used for long-term or on-demand contraception. For long-term contraception, the pill is intended to be used daily for 3 weeks followed by a pill-free week. For on-demand or emergency contraception, the pill is intended to be used daily up to 5 days after vaginal intercourse during the fertile period of the menstrual cycle. Inactive compounds may comprise any combination of dyes, water, corn starch, magnesium stearate, lactose, croscarmellose sodium, polyethylene glycol and titanium dioxide. The purpose of these ingredients is to stabilize the composition of the pill and to assist in dissolving the active compound(s) in the gastrointestinal tract.

[026] The following examples demonstrate that triterpenoids can prevent hormone-induced or fallopian tubal fluid-induced activation of the sperm calcium channel, avert sperm hyperactivation, decrease sperm motility and inhibit sperm fertility.

[027] **Plant triterpenoids including pristimerin and lupeol significantly reduce the activation of CatSper by either P4 or PregS.** 2-AG hydrolysis by monoacyl lipases, such as ABHD2, is required for CatSper activation. The plant triterpenoid pristimerin was reported to inhibit the activity of related monoacylglycerol lipase (MAGL) (9). If pristimerin can also inhibit ABHD2, then sperm exposure to this compound should prevent CatSper activation by P4 or PregS. To test this hypothesis, human spermatozoa were stimulated with pristimerin, followed by exposure to either a mixture of pristimerin and P4, or to a mixture of pristimerin and PregS. In these experiments we analyzed inward monovalent currents through CatSper ($I_{CatSper}$) of human sperm. Electrophysiology recordings were performed as described in (14). The mere presence of pristimerin did not affect basal $I_{CatSper}$, which indicates that pristimerin did not target the channel directly. However, co-application of pristimerin with P4 or PregS significantly reduced CatSper activation. Compared to stimulation with P4 or PregS alone, the $I_{CatSper}$ stimulation was reduced by 63% (pristimerin and P4) and by 48% (pristimerin and PregS) (7).

[028] Another pharmacologically active plant triterpenoid, which affects sperm functions when orally administered to rats, is lupeol (8). Lupeol is similar in structure to steroid hormones. Comparable to pristimerin, lupeol alone did not affect basal $I_{CatSper}$. However, administration of lupeol with P4 or PregS led to an even stronger inhibition of $I_{CatSper}$ than pristimerin. Compared to CatSper stimulation elicited by P4 or PregS alone, CatSper currents were reduced by 71% and 68%, respectively, in combination with P4 or PregS (7). We have also shown with calcium imaging that pristimerin dose-dependently blocked steroid-activated CatSper activation in human spermatozoa.

[029] **Pristimerin and lupeol decrease sperm hyperactivation in the presence of P4.**

Hyperactivated sperm motility is characterized by a highly asymmetrical bending of the sperm tail due to a CatSper-mediated rise in flagellar calcium concentration (15). Curvilinear velocity (VCL) is the average velocity of the sperm head through the sperm trajectory, which increases during capacitation. A CatSper-mediated calcium rise promotes hyperactivation and makes the sperm trajectory less linear, which results in an increase of VCL. Capacitation increases CatSper activity, which results in a higher percentage of sperm with hyperactivated motility. Thus, capacitated spermatozoa tend to have higher VCL values than non-capacitated. Since both P4 and PregS activate CatSper, while pristimerin and lupeol inhibit it, we explored whether VCL values of human sperm are affected in the presence of plant triterpenoids or steroid hormones. As expected, neither of the compounds changed VCL values of non-capacitated sperm cells. In capacitated spermatozoa, P4 stimulation increased VCL by 12%, comparable to numbers reported by others (3, 16), but VCL values remained unchanged in the presence of PregS, pristimerin or lupeol alone (7). When spermatozoa were stimulated with P4+pristimerin or P4+lupeol, VCL values were reduced by 39% and 48%, respectively, in comparison to VCL values obtained in the presence of P4, and the reduced VCL values were comparable to those of non-capacitated cells. Stimulating capacitated sperm with PregS in combination with pristimerin or lupeol decreased VCL by 18% and 9%, respectively, compared to sperm, which were treated with PregS alone. VCL values of non-capacitated sperm remained unchanged under such conditions. Since CatSper is not only required for hyperactivation but also for basal motility, we sought to determine whether pristimerin and lupeol also affect sperm motility. The number of both capacitated and non-capacitated motile spermatozoa remained unchanged when stimulated with either compounds. However, when P4 was co-applied with pristimerin or lupeol the percentage of motile capacitated sperm decreased significantly by 19%, respectively, whereas the values of non-capacitated cells did not change. Co-stimulation with PregS and pristimerin or lupeol, however, did not result in a significant reduction of motile capacitated or non-capacitated sperm. These results indicate that triterpenoids like pristimerin and lupeol have the capacity to significantly reduce sperm hyperactivation by blocking the P4-mediated activation of CatSper.

[030] Intravaginal spermicidal triterpenoid formulations

[031] Formulations encompass a representative spermicidal triterpenoid, including pristimerin, lupeol or both compounds (e.g. 50:50 w/w combinations).

[032] A) Intravaginal spermicidal triterpenoid aerosol foam (canister with applicator); active ingredient: spermicidal triterpenoid, 10% inactive ingredients: benzoic acid, cellulose gum, acetyl alcohol, fragrance, glacial acetic acid, methylparaben, phosphoric acid, polyvinyl alcohol, propellant A-31, propylene glycol, purified water, sorbic acid, stearamidoethyl diethyl amine,

stearic acid.

[033] B) Intravaginal spermicidal triterpenoid gel (prefilled applicators, 0.1 oz (2.6g) each; active ingredients: spermicidal triterpenoid, 5%; inactive ingredients: lactic acid, methylparaben, povidone, propylene glycol, water (purified), sodium carboxy methyl cellulose, sorbic acid, sorbitol

[034] C) Vaginal spermicidal triterpenoid contraceptive sponge; active ingredients: in each sponge: spermicidal triterpenoid (1000 mg); inactive ingredients: benzoic acid, citric acid, sodium dihydrogen citrate, sodium metabisulfite, sorbic acid, water in a polyurethane foam sponge.

[035] D) Vaginal spermicidal triterpenoid contraceptive film; active ingredient: spermicidal triterpenoid (30%); inactive ingredients: glycerin, polyvinyl alcohol, purified water.

[036] References

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CLAIMS:

1. A pharmaceutical composition comprising a spermicidal triterpenoid formulated and configured as an intravaginal or systemic contraceptive.

2. The composition of claim 1 formulated and configured in form of a vaginal contraceptive foam, cream or gel, and the triterpenoid is in a predetermined, unit or multi-unit dosage effective for contraception.

3. The composition of claim 1 formulated and configured in unit form of a vaginal contraceptive film (VCF), suppository, sponge, slow release intravaginal devices or intrauterine devices such as drug-impregnated silicone elastomer vaginal rings or polymeric IUDs, and the triterpenoid is in a predetermined, unit dosage effective for contraception.

4. The composition of claim 1 formulated and configured in form of a systemic contraceptive that is a pill, transdermal or hypodermal patch, and the triterpenoid is in a predetermined, unit or multi-unit dosage effective for contraception.

5. The composition of any of claims 1-4, wherein the triterpenoid inhibits human tubular fluid, progesterone (P4)- or pregnenolone sulfate (PregS)-induced activation of the principal human sperm calcium channel, CatSper, such as indicated by calcium imaging or recording of inward monovalent currents ($I_{CatSper)}$ through the channel with electrophysiology or calcium imaging.

6. The composition of any of claims 1-5, wherein the triterpenoid inhibits P4- or PregS-induced human sperm hyperactivation, sperm motility or fertilization.

7. The composition of any of claims 1-6 wherein the triterpenoid is at least one of: a plant triterpenoid, a pentacyclic triterpenoid, a triterpenoid quinone methide and a 11-unsubstituted (11-H) triterpenoid.

8. The composition of any of claims 1-7, wherein the triterpenoid comprises ring structure of pristimerin or lupeol, or is a derivative thereof, such as celastrol.

9. The composition of any of claims 1-4 wherein the triterpenoid is pristimerin.

10. The composition of any of claims 1-4 wherein the triterpenoid is lupeol.

11. A method of using a composition of any of claims 1-3 or 5-10, comprising delivering the composition to a vagina.

12. A method of using a composition of any of claims 1 or 4, comprising delivering the composition via an oral route, transdermal or hypodermal route.

13. A method of inhibiting sperm motility comprising contacting the sperm with an effective amount of a spermicidal triterpenoid.

14. The method of claim 14 wherein the triterpenoid is formulated and configured as compositions according to any of claims 1-10.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/012015

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/00; A61K 31/00; A61P 15/00 (2018.01)
CPC - A61K 9/0034; A61K 9/0036; A61K 31/00; A61P 15/00 (2018.02)

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)
See Search History document

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)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2005/0208147 A1 (VIJAY et al) 22 September 2005 (22.09.2005) entire document	1-3, 13 --- 4, 5, 9, 10, 12
Y	EP 2 698 155 A1 (LUNAMED AG) 19 February 2014 (19.02.2014) entire document	4, 9, 10, 12
Y	LISHKO et al., Progesterone activates the principal Ca2+ channel of human sperm, Nature, Vol. 471, 17 March 2011, Pgs. 387-391	5
P, X	MANNOWETZ et al., Regulation of the sperm calcium channel CatSper by endogenous steroids and plant triterpenoids, Proceedings of the National Academy of Sciences of the United States of America, Vol. 114, No. 22, 30 May 2017 [retrieved on 06 February 2018]. Retrieved from the internet: <URL: http://www.pnas.org/content/pnas/114/22/5743.full.pdf> Pgs. 5743-5748	1-5, 9, 10, 12, 13

☐ 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 application or patent but published on or after the international filing date
"L" document which may throw doubts on priority 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
"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
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 February 2018	07 MAR 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/012015

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-8, 11, 14
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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

2. ☐ As all searchable claims could be searched without effort justifying additional fees, 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 a protest fee.

☐ The additional search fees were accompanied by the applicant's 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.