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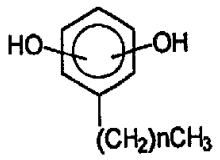
(54) Title: TOPICAL MEDICAMENT COMPRISING PHENOLIC BIOCIDE AND CHOLINE

(57) Abstract

The use of a phenolic biocide, which is preferably a compound of formula (I), in which n is from 0 to 19, in combination with choline or a derivative or a salt thereof, for the preparation of a topical medicament for the treatment of warts, corns and verucae.



(I)

TOPICAL MEDICAMENT COMPRISING PHENOLIC BIOCIDE AND CHOLINE

The present invention relates to the preparation of topical medicaments for the treatment of warts and related conditions. In particular it relates to the use of phenolic biocidal compounds to prepare such medicaments.

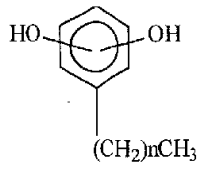
A wide range of generally non-life threatening but highly irritating conditions affect both the human and animal skin. These include warts, corns and verucae.

A range of compounds have been suggested for use in the treatment of such conditions, however they all suffer from one or more drawbacks, including lack of efficacy or excessive irritancy. Thus there is a continuing need for a treatment of warts, corns and verucae which is both effective and non-irritant.

We have now found that a range of phenolic biocidal compounds are particularly effective at treating such conditions and that their irritancy can be sufficiently reduced by combination with choline or derivatives thereof.

According to a first aspect the present invention provides the use of a phenolic biocide in combination with choline or a derivative or a salt thereof, for the preparation of a topical medicament for the treatment of warts, corns and verucae.

According to a second aspect the present invention provides the use of a compound of formula I



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in which n is from 0 to 19, in combination with choline or a derivative or a salt thereof, for the preparation of a topical medicament for the treatment of warts, corns and verucae.

There is further provided a topical medicament comprising a phenolic biocide, which is preferably a compound of formula I in which n is from 0 to 19, and choline or a derivative or a salt thereof.

Preferably in the topical medicaments of the invention the phenolic biocide and the choline or derivative or salt thereof are in intimate admixture.

Preferably in the compound of formula I n is 3 to 13.

Most preferably the compound of formula I is 4-hexylresorcinol.

According to a third aspect the present invention provides use of 4-hexylresorcinol in combination with choline or a derivative or a salt thereof for the preparation of a topical medicament for the treatment of warts, corns and verucae.

According to a fourth aspect the present invention provides a topical medicament comprising:

i) a compound of formula I in which n is from 0 to 19,

ii) choline, or a derivative or a salt thereof, and

iii) a surfactant;

with the proviso that the derivative is other than lecithin.

According to a fifth aspect the present invention provides a topical medicament comprising:

i) 0.01 to 20% w/w of a compound of formula I in which n is from 0 to 19,

ii) 0.01 to 20% w/w choline, or a derivative or a salt thereof, and

iii) 0.1 to 5% w/w of a surfactant;

with the proviso that the derivative is other than lecithin.

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The compound of formula I is preferably used at a concentration of from 0.01 to 20% by weight, more preferably 0.1 to 5% w/w, most preferably 0.2 to 3.0% w/w.

Preferred derivatives of choline include glycerophosphocholine and acetylcholine. Preferred salts of choline include choline chloride, choline phosphate, choline iodide and choline bromide, most preferably choline chloride.

The concentration of choline, or a derivative, or a salt thereof, in the topical medicaments of the invention is preferably from 0.01 to 20% w/w, more preferably 0.1 to 5% w/w, most preferably 0.2 to 3.0% w/w. When lecithin is used in the topical medicaments the concentration is preferably 0.2 to 30% w/w, most preferably 1 to 10% w/w.

We have also found that the inclusion of a surfactant in the topical medicaments of the invention may lead to improved activity versus warts, corns and verucae.

Therefore the topical medicaments of the invention preferably further comprise a surfactant. The surfactant is preferably an anionic surfactant, most preferably N-lauroylsarcosine or a salt thereof. The concentration of surfactant in the topical medicaments of the invention is preferably from 0.1 to 5% w/w, most preferably from 0.2 to 3% w/w.

The topical medicaments of the invention may also comprise further biocidal agents in addition to the compounds of formula I. Preferably these further biocides are quaternary ammonium compounds or phenolic compounds. More preferably the further biocide is trimethyltetradecylammonium bromide (cetrimide).

The concentration of the further biocide in the topical medicaments of the invention is preferably from 0.1 to 5% w/w, most preferably from 0.2 to 3% w/w.

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The topical medicaments of the invention may also comprise inositol. The concentration of inositol is preferably from 0.05 to 20% w/w; most preferably from 0.2 to 5% w/w.

According to a sixth aspect the present invention provides a topical medicament comprising:

Hexylresorcinol	1.8 g
Choline Chloride	1.0 g
White vaseline	97.2 g

According to a seventh aspect the present invention provides a topical medicament comprising:

Hexylresorcinol	1.8 g
Choline Chloride	1.0 g
N-lauroylsarcosine sodium	1.8 g
White vaseline	95.4 g

According to an eighth aspect the present invention provides a topical medicament comprising:

Hexylresorcinol	1.8 g
N-lauroylsarcosine sodium	1.8 g
Cetrimide	0.5 g
Choline Chloride	1.0 g
Myo-inositol	0.25 g
White vaseline	94.65 g

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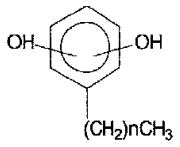
The topical medicaments of the invention may be applied to any part of the body surface, including mucous membranes. The topical medicaments of the invention may be applied in conventional cream or ointment form; may be applied predispersed onto a dressing or plaster; or in conventional topical sustained release devices.

In a ninth aspect of the present invention there is provided a method of treating warts, corns or verucae comprising topically treating a subject requiring such treatment with a phenolic biocide in combination with choline or a derivative or a salt thereof.

In a tenth aspect of the present invention there is provided a method for the treatment of warts, corns or verucae comprising topically administering to a subject requiring such treatment a compound of formula I in combination with choline or a derivative or a salt thereof and wherein said compound is as follows:



in which n is from 0 to 19.

According to an eleventh aspect the present invention provides a method for the treatment of warts, corns or verucae comprising topically administering to a subject requiring such treatment 4-hexylresorcinol in combination with choline or a derivative or a salt thereof.

Unless the context clearly requires otherwise, throughout the description and the claims, the words 'comprise', 'comprising', and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

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The topical medicaments of the invention may be formulated using any suitable aqueous or non-aqueous vehicles, the preferred vehicles are paraffin, Vaseline (a trademark), Lanette N (a mixture of cetearyl alcohol and sodium cetearyl alcohol sulphate), and non aqueous polymer compositions including nitrocellulose, Collodion and Carboset (available from B.F. Goodrich) and ethylcellulose. Preferably the vehicle is non-aqueous.

The topical medicaments of the invention may be manufactured using any conventional manufacturing process, however it is preferred that the phenolic biocide and the choline or derivative or salt thereof are in intimate admixture. This may be ensured either by homogenous premixing of the phenolic biocide and the choline or derivative or salt thereof before dispersion in the vehicle, or by thorough dispersion of both ingredients directly into the vehicle.

In a related embodiment there is provided a topical medicament comprising:

i) 0.01 to 20% w/w of a compound of formula I in which n is from 0 to 19,

ii) 0.01 to 20% w/w choline, or a derivative or a salt thereof, and

iii) 0.1 to 5% w/w of a surfactant.

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The invention will now be illustrated by reference to the following examples.

Example 1

The following formulation is prepared

Hexylresorcinol (Sigma H6250)	1.8g
Choline chloride (Sigma C1879)	1.0g
White Vaseline	97.2g

The hexylresorcinol and choline chloride are pulverised and mixed together, then added to the Vaseline and homogenised by rapid stirring with a spatula.

Example 2

The following formulation is prepared

Hexylresorcinol (Sigma H6250)	1.8g
Choline chloride (Sigma C1879)	1.0g
N-lauroylsarcosine sodium (Sigma L5000)	1.8g
White Vaseline	95.4g

The hexylresorcinol, choline chloride and N-lauroylsarcosine sodium are pulverised and mixed together, then added to the Vaseline and homogenised by rapid stirring with a spatula.

Comparative Example 1

Example 1 is repeated with the following formula:

Hexylresorcinol (Sigma H6250)	1.8g
White Vaseline	98.2g

Comparative Example 2

Example 2 is repeated with the following formula:

Hexylresorcinol (Sigma H6250)	1.8g
N-lauroylsarcosine sodium (Sigma L5000)	1.8g
White Vaseline	96.4g

Example 3

The following formulation is prepared

Hexylresorcinol (Sigma H6250)	1.8g
N-lauroylsarcosine (Sigma L5000)	1.8g
Cetrimide (Federa P68 1932)	0.5g
Choline chloride (Sigma C1879)	1.0g
Myo-inositol (Sigma I 5125)	0.25g
White Vaseline	94.65g

All the powders are pulverised and mixed together. Vaseline is added and the mixture is homogenised by rapid stirring with a spatula.

Example 4

Corn Treatment

A female patient having an irritant corn on the outside of the small toe (previously resistant to all conventional treatments for at least 5 years) was treated by application of the composition of Example 3 to the corn. The application was of a liberal sample twice daily for 10 days and once daily for 5 days. The corn was covered by a conventional corn plaster between applications. After 15 days the corn was completely healed with no scarring and no pain. There has been no relapse after 3 months.

Example 5

Veruca Treatment

A male patient having a veruca on the sole of one foot was treated by application of the composition of Example 3 to the veruca. The application was of from 0.1 to 0.2 ml of the composition twice daily for 21 days. The veruca was covered with a conventional plaster between applications. After 21 days the veruca was healed (removed) leaving no pain or scarring. No relapse has occurred after 12 months.

Example 6

The ability of choline chloride to reduce the irritant properties of hexylresorcinol alone or in combination with N-lauroylsarcosine sodium (an anionic surfactant) was tested by the following procedure.

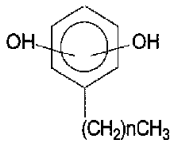
Four 2 cm^2 sites were marked at intervals along the intact skin of the forearm of an adult human female. Samples of each of Examples 1 and 2 and comparative examples 1 and 2 were applied liberally to each site (one treatment per site). Application was carried out twice daily for 3 days (six applications in all). The sites were occluded using adhesive plasters between applications. The appearance of the sites on the arm was inspected 72 hours after the first application with the following results.

Comparative Example 1	- blistering, skin irritation
Example 1	- no blistering, skin unmarked
Comparative Example 2	- blistering, skin irritation
Example 2	- no blistering, skin mostly clear, reduced irritation.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. The use of a phenolic biocide in combination with choline or a derivative or a salt thereof, for the preparation of a topical medicament for the treatment of warts, corns and verucae.

2. The use of a compound of formula I



in which n is from 0 to 19,

in combination with choline or a derivative or a salt thereof for the preparation of a topical medicament for the treatment of warts, corns and verucae.

3. The use of 4-hexylresorcinol in combination with choline or a derivative or a salt thereof for the preparation of a topical medicament for the treatment of warts, corns and verucae.

4. The use of any one of claims 1 to 3 wherein the salt of choline is selected from choline chloride, choline phosphate, choline iodide and choline bromide.

5. The use of any one of claims 1 to 3 wherein the derivative of choline is other than lecithin.

6. The use of any one of claims 1 to 3 wherein the derivative of choline is selected from the group consisting of glycerophosphocholine and acetylcholine.

7. A topical medicament comprising:

(i) a compound of formula I,

(ii) choline, or a derivative or a salt thereof, and

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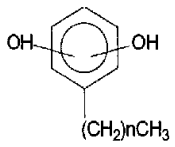
(iii) a surfactant;

with the proviso that the derivative is other than lecithin, and wherein the compound of formula I is as follows:



in which n is from 0 to 19.

8. A topical medicament as claimed in claim 7 wherein the compound of formula 1 is 4-hexylresorcinol.

9. A topical medicament as claimed in claim 7 or claim 8 wherein the derivative of choline is selected from the group consisting of glycerophosphocholine and acetylcholine.

10. A topical medicament as claimed in claim 7 or claim 8 wherein the salt of choline is selected from choline chloride, choline phosphate, choline iodide and choline bromide.

11. A topical medicament as claimed in any one of claims 8 to 10 wherein the surfactant is N-lauroylsarcosine or a salt thereof.

12. A topical medicament comprising

(i) 0.01 to 20% w/w of a compound of formula I in which n is from 0 to 19,

(ii) 0.01 to 20% w/w choline, or a derivative or a salt thereof, and

(iii) 0.1 to 5% w/w of a surfactant;

with the proviso that the derivative is other than lecithin, and wherein the compound of formula I is as follows:

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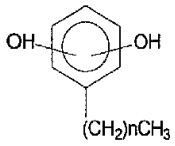

in which n is from 0 to 19.

13. A topical medicament as claimed in claim 12 wherein the compound of formula I is 4-hexylresorcinol.

14. A topical medicament as claimed in claim 12 or 13 wherein the derivative of choline is selected from the group consisting of glycerophosphocholine and acetylcholine.

15. A topical medicament as claimed in claim 12 or 13 wherein the salt of choline selected from choline chloride, choline phosphate, choline iodide and choline bromide.

16. A topical medicament as claimed in any one of claims 12 to 15 wherein the surfactant is N-lauroylsarcosine or a salt thereof.

17. A topical medicament comprising:

Hexylresorcinol	1.8 g
Choline Chloride	1.0 g
White vaseline	97.2 g

18. A topical medicament comprising:

Hexylresorcinol	1.8 g
Choline Chloride	1.0 g
N-lauroylsarcosine sodium	1.8 g
White vaseline	95.4 g

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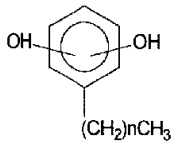
19. A topical medicament comprising:

Hexylresorcinol	1.8 g
N-lauroylsarcosine sodium	1.8 g
Cetrimide	0.5 g
Choline Chloride	1.0 g
Myo-inositol	0.25 g
White vaseline	94.65 g

20. A method of treating warts, corns or verucae comprising topically treating a subject requiring such treatment with a phenolic biocide in combination with choline or a derivative or a salt thereof.

21. A method for the treatment of warts, corns or verucae comprising topically administering to a subject requiring such treatment a compound of formula I in combination with choline or a derivative or a salt thereof and wherein said compound is as follows:



in which n is from 0 to 19.

22. A method for the treatment of warts, corns or verucae comprising topically administering to a subject requiring such treatment 4-hexylresorcinol in combination with choline or a derivative or a salt thereof.

23. A method of any one of claims 20 to 22 wherein the salt of choline is selected from choline chloride, choline phosphate, choline iodide and choline bromide.

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24. A method of any one of claims 20 to 22 wherein the derivative of choline is other than lecithin.

25. A method of any one of claims 20 to 23 wherein the derivative of choline is selected from the group consisting of glycerophosphocholine and acetylcholine.

26. A topical medicament comprising a compound of formula I, a surfactant and choline or a salt of choline or a derivative of choline other than lecithin, substantially as hereinbefore described with reference to one or more of the Examples.

27. The use of a phenolic biocide in combination with choline or a derivative or a salt of choline in the preparation of a topical medicament for the treatment of warts, corns and verucae, substantially as hereinbefore described with reference to one or more of the Examples.

28. The use of a compound of formula I in combination with choline or derivative or salt of choline in the preparation of a topical medicament for the treatment of warts, corns and verucae, substantially as hereinbefore described with reference to one or more of the Examples.

29. The use of 4-hexylresorcinol in combination with choline or a derivative or a salt of choline in the preparation of a topical medicament for the treatment of warts, corns and verucae, substantially as hereinbefore described with reference to one or more of the Examples.

30. A topical medicament comprising a compound of formula I, a surfactant and choline or a derivative of choline or a salt of choline, with the proviso that said

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derivative is other than lecithin, substantially as hereinbefore described with reference to one or more of the Examples.

31. A method for the treatment of warts, corns or verucae comprising topically treating a subject requiring such treatment with a phenolic biocide in combination with choline or a derivative or a salt thereof, substantially as hereinbefore described with reference to one or more of the Examples.

32. A method for the treatment of warts, corns or vercuae comprising topically administering to a subject requiring such treatment a compound of formula I in combination with choline or a derivative or a salt thereof, substantially as hereinbefore described with reference to one or more of the Examples.

33. A method for the treatment of warts, corns or verucae comprising topically administering to a subject requiring such treatment a compound of formula I in combination with choline or a derivative or a salt thereof, substantially as hereinbefore described with reference to one or more of the Examples.

34. A method for the treatment of warts, corns, or verucae comprising topically administering to a subject 4-hexylresorcinol in combination with choline or a derivative or salt thereof, substantially as hereinbefore described with reference to one or more of the Examples.

DATED this 23rd day of June 2000
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