

**FORMULATIONS WITH SANGUINARINE, CHELERYTHRINE OR CHELIDONINE
FOR THE TREATMENT OF WARTS, VERRUCAS AND
PSORIATIC PLAQUES**

Summary

The present invention relates to pharmaceutical formulations useful in the treatment of common skin warts and verrucas, anal and vulvar warts and psoriatic plaques.

The formulations of the invention contain free or salified
5 benzophenanthridine alkaloids and suitable vehicles, depending on the area to be treated. Said alkaloids possess a potent antiproliferative, antibacterial, antifungal, analgesic, antiangiogenic and anti-inflammatory action which makes them useful for the treatment of warts, verrucas and psoriasis.

Vegetable oils rich in polyunsaturated acids are used as vehicles to
10 facilitate the absorption of alkaloids.

Technical Background

Warts and verrucas are the result of infections of the epithelia of the skin and mucous membranes by human papillomavirus and cytomegalovirus, and can be considered as neoplasms. These infections can be associated with a
15 wide variety of benign and malignant tumours, and therefore require suitable treatment. Warts, depending on the type of infecting virus, are usually present in all parts of the body, on the hands and face, and especially in the anogenital region. Anogenital warts usually invade the skin and the proximal mucosa. In circumcised men and male homosexuals, the glans and urethral meatus are
20 also involved. In women, these warts can degenerate to fibroepitheliomas and a variety of benign or malignant mucocutaneous tumours. In many cases the complications of warts include severe itching, occasional bleeding, and often bacterial and fungal infections. Another widespread form of warts affects elderly people; these warts are located on the face, neck and chest, causing an

unsightly appearance and functional impairment.

Patients who suffer from warts and verrucas often develop anxiety and depression. The current treatments for this disorder, which are not always completely effective, involve the use of viral antimetabolites such as 5-fluorouracyl, or products like podophyllotoxin and interferon, applied topically and systemically, with mediocre results. A tea extract for the treatment of warts and verrucas, requiring topical application for months, was recently approved in the United States of America. The first-line treatment for external warts and verrucas is still surgical, involving ablation of the removable mass and repetition of the treatment several times to ensure thorough eradication. Several months is an unacceptably long time to eradicate the disease, bearing in mind how contagious it is.

The first-line treatment for psoriatic plaques generally consists of using products with a keratolytic and emollient action which, however, do not cure the problem. The use of corticosteroids is not generally recommended because of their known side effects.

One of the plants which has been most widely studied is *Sanguinaria canadensis*, already used by native Americans to treat tumours and skin sores. Numerous alkaloids, such as sanguinarine, chelerythrine, chelidonine and other minor ones, which are also common in other *Papaveraceae*, have been isolated from this plant, especially its roots.

All these plants have been studied since the beginning of this century in view of their use as medicinal plants in folk medicine. Yellow latex of *Chelidonium majus* was used in the past to treat warts, verrucas and benign skin tumours; however, its use has long been discontinued because of significant tolerability problems. The most widespread use of these alkaloids, especially chelidonine, was to treat infectious diseases such as tuberculosis, or protozoa such as leishmaniasis and malaria; however, their systemic toxicity

prevented their long-term use.

The use of benzophenanthridine alkaloids or salts thereof for the preparation of medicaments for the treatment of tumours is disclosed in Italian patent application no. MI2008A284, filed on 20 February 2008 by the same
5 Applicant. The use of benzophenanthridine alkaloids chosen from sanguinarine, chelerythrine or chelidonine is disclosed in particular.

Italian patent application no. MI2008A38, filed on 11 January 2008 by the same Applicant, describes formulations containing sanguinarine or chelerythrine, or their salts or extracts containing them, for the treatment and
10 prevention of mucositis, especially mucositis induced by chemotherapy, radiotherapy or immunosuppressant treatment.

Description of the Invention

It has now surprisingly been found that the benzophenanthridine alkaloids sanguinarine, chelerythrine and chelidonine, in free or salified form,
15 can be used advantageously to treat common skin warts and verrucas (including those typical of elderly people), anal and vulvar warts, and psoriatic plaques.

The invention therefore provides formulations containing sanguinarine, chelerythrine or chelidonine or their salts or extracts containing them, mixed
20 with suitable vehicles and/or excipients, for the treatment of common skin warts and verrucas, anal and vulvar warts, and psoriatic plaques.

Sanguinarine, chelerythrine and chelidonine may be present in substantially pure form or in the form of extracts of *Sanguinaria canadensis*, *Macleaya cordata* or *Macleaya macrocarpa*, or *Chelidonium majus*.

25 The invention also relates to the use of sanguinarine, chelerythrine or chelidonine, or salts or extracts containing them, for the preparation of medicaments for the treatment of common skin warts and verrucas, anal and vulvar warts, and psoriatic plaques.

The formulations according to the invention, administered by locoregional application, rapidly eliminate warts, verrucas and psoriatic plaques, without irritating the surrounding tissue. The treatments cure the disease in less than a month, without causing side effects which require the
5 discontinuance of the treatment.

It has also been found that the salts of these alkaloids with luteic acid are particularly effective for the purposes of this invention. Said salts are prepared by reacting the sulphates or chlorides of the alkaloids with luteic acid sodium or potassium salt, and subsequent crystallisation.

10 The formulations of the invention can also contain procyanidins, as such or in the form of extracts containing them, to strengthen the antiviral activity.

According to a preferred aspect, therefore, the formulations of the invention may contain procyanidolic compounds, in particular extract of *Vitis*
15 *vinifera* and procyanidin A2, B2 and B6. According to a particularly preferred aspect, the formulations of the invention will be combined with proanthocyanidin A2.

Moreover, as of warts, verrucas and psoriasis often cause itching, the alkaloids according to the invention can be combined with isobutylamides of
20 polyunsaturated acids or extracts containing them, which reduce peripheral pain and itching due to their ability to bind cannabinoid CB1 and CB2 receptors. The combination of alkaloids with isobutylamides operates synergically by eliminating the warts and verrucas, inflammation in the area affected by the virus, and itching, which in some cases makes social life
25 difficult.

Consequently, according to a further preferred aspect, the formulations of the invention may also contain a lipophilic extract of *Zanthoxylum bungeanum* or *Echinacea angustifolia*, or single isobutylamides such as

pellitorine.

According to a preferred aspect, the formulations of the invention will preferably contain sanguinarine, chelerythrine or chelidonine, in free or salified form, in quantities ranging between 0.1 mg and 1 mg per square
5 centimetre of human skin.

According to a preferred aspect, the formulations of the invention will preferably contain between 0.01 mg and 0.1 mg of said isobutylamides, as such or in the form of extracts containing them.

According to a preferred aspect, the formulations of the invention may
10 be formulated in water/oil emulsions or in oils rich in polyunsaturated fatty acids, particularly ω -3, such as the oils of *Enothera biennis*, *Linum usatissimum*, *Ribes nigrum* and the like, which increase the tissue and cell permeation of the active constituents.

The formulations of the invention can be prepared according to well-
15 known conventional methods, such as those described in "Remington's Pharmaceutical Handbook", Mack Publishing Co., N.Y., USA, together with suitable excipients. Examples of formulations according to the invention include creams, ointments, powders, lotions and the like.

For internal warts, the compounds according to the invention can be
20 formulated as vaginal pessaries or suppositories or equivalent formulations for vaginal or anal treatment, including capsules that dissolve at internal body temperature.

For the treatment of psoriasis with keratinised plaques, the formulations will be based on excipients that keep the affected area moisturised.

25 The examples set out below illustrate the invention.

Example 1 - Oily suspension for soft gelatin capsules designed to be inserted in the vaginal meatus

	<i>Macleaya cordata</i> lipophilic extract (75%)	15 mg
	Procyanidin A2	20 mg
5	<i>Echinacea angustifolia</i> isobutylamides	0.5 mg
	Soya lecithin	50 mg
	Beeswax	50 mg
	Vegetable oil q.s. for	800 mg

10 **Example 2 - Cream (oil-in-water emulsion)**

	Chelidonine luteate	200.00 mg
	Procyanidin A2	400.00 mg
	<i>Zanthoxylum bungeanum</i> lipophilic extract	200.00 mg
	Propylene glycol	10.00 g
15	Isopropyl myristate	5.00 g
	Cetyl alcohol	5.00 g
	Polysorbate	3.00 g
	Carbomer	0.40 g
	Methyl p-hydroxybenzoate	0.10 g
20	Propyl p-hydroxybenzoate	0.05 g
	Purified water q.s. for	100 g

Example 3 - Vaginal pessary

	<i>Macleaya</i> alkaloid fraction	3.0 mg
25	Proanthocyanidin A2	20.0 mg
	<i>Echinacea angustifolia</i> isobutylamides	0.5 mg
	Glycerides of fatty acids q.s. for	2.0 g

Example 4 - Psoriasis ointment

	<i>Macleaya</i> alkaloid fraction	300.00 mg
	<i>Vitis vinifera</i> total procyanidins	300.00 mg
	Propylene glycol	10.00 g
5	Isopropyl myristate	3.00 g
	<i>Enothera biennis</i> oil	2.00 g
	Cetyl alcohol	5.00 g
	Polysorbate	3.00 g
	Carbomer	0.40 g
10	Methyl p-hydroxybenzoate	0.10 g
	Propyl p-hydroxybenzoate	0.05 g
	Purified water q.s. for	100.00 g

CLAIMS

1. Formulations containing sanguinarine, chelerythrine or chelidonine or their salts or extracts containing them, mixed with suitable vehicles and/or
5 excipients for the treatment of common skin warts and verrucas, anal and vulvar warts and psoriatic plaques.
2. Formulations as claimed in claim 1, containing sanguinarine.
3. Formulations as claimed in claim 1, containing chelerythrine.
4. Formulations as claimed in claim 1, containing chelidonine.
- 10 5. Formulations as claimed in claim 1, containing extracts of *Sanguinaria canadensis*, *Macleaya cordata* or *Macleaya macrocarpa*, or *Chelidonium majus*.
6. Formulations as claimed in claim 1, wherein the sanguinarine, chelerythrine or chelidonine are in the form of a salt with luteic acid.
- 15 7. Formulations as claimed in any of claims 1 to 6, also containing procyanidolic compounds chosen from extract of *Vitis vinifera*, procyanidin A2, B2 and B6, and proanthocyanidin A2.
8. Formulations as claimed in claim 7, containing proanthocyanidin A2.
9. Formulations as claimed in any of claims 1 to 8, also containing natural
20 or synthetic isobutylamides.
10. Formulations as claimed in claim 9, wherein the isobutylamides are contained in a lipophilic extract of *Zanthoxylum bungeanum* or *Echinacea angustifolia*.
11. Formulations as claimed in claim 9, wherein the isobutylamides consist
25 of pellitorine.
12. Formulations as claimed in any of claims 1 to 10 in the form of creams, ointments, powders, lotions, vaginal pessaries or suppositories, capsules that dissolve at internal body temperature, or equivalent formulations.

13. Use of sanguinarine, chelerythrine or chelidonine, or their salts or extracts containing them, for the preparation of medicaments for the treatment of the common skin warts and verrucas, anal and vulvar warts and psoriatic plaques.

5 14. Use as claimed in claim 13, wherein the sanguinarine, chelerythrine or chelidonine are salified with luteic acid.

15. Use as claimed in one or more of claims 13 and 14 combined with procyanidolic compounds chosen from extract of *Vitis vinifera*, procyanidin A2, B2 and B6, and proanthocyanidin A2.

10 16. Use as claimed in one or more of claims 13 to 15, combined with natural or synthetic isobutylamides.