

**FORMULATIONS FOR THE TREATMENT OF MUCOSITIS
INDUCED BY ANTITUMOR OR IMMUNOSUPPRESSIVE THERAPY**

The present invention relates to pharmaceutical formulations useful in the treatment of mucositis induced in humans by chemotherapy, radiotherapy and treatment with systemic immuno-suppressors.

The formulations of the invention contain free or salified
5 benzophenanthridine alkaloids and suitable carriers, depending on the various parts of the patient body to treat. Said alkaloids have strong antimicrobial, antifungal, anti-inflammatory, analgesic, immunostimulating, antiangiogenetic and an antiproliferative action selective for cancer cells and are capable of reducing or preventing mucositis.

10 The invention further relates to the salts of said alkaloids with luteic acid.

Technological background

Severe forms of painful mucositis often occur both in oncology and organ or bone marrow transplantation with concomitant immunosuppressive
15 therapy. They can only be counteracted by systemic analgesics, in particular opioids, combined with heavy support therapies. In many cases, onset of severe mucositis is the cause of suspension of chemotherapeutic treatments, thus allowing the tumor to continue its growth.

Radical treatments can induce side effects mainly affecting the
20 gastrointestinal tract, particularly the mouth, esophagus, stomach, intestine and in some cases even the genito-urinary tract.

Medicaments which most frequently induce mucositis are anthracyclines, fluorouracil and analogues; and others, such as taxol, actinomycin, mithramycin, etoposide, topotecan, amsacrine, methotrexate,
25 hydroxyurea, alone or in combination with other chemotherapeutics such as

platinum complexes commonly used in cancer therapy. The combination of chemo- and radio-therapy in some districts, such as in head and neck therapy, causes mucositis in 95% of treated patients.

Conventional treatments for mucositis involve the administration of non-gastrolesive anti-inflammatory agents, analgesics, antimicrobials, antifungals, H₂ antagonists and protective gels which help to maintain the affected area hydrated. Local pain is a side-effect which restricts the rational administration of the other drugs. The patient under such conditions experiences difficulty to eat, which leads to weight loss, dehydration and severe health impairment.

Disclosure of the invention

It has now surprisingly been found that the benzophenanthridine alkaloids sanguinarine and chelerythrine are advantageously effective in reducing and/or preventing the onset of mucositis induced by oncological or immunosuppressive treatment.

Therefore the invention provides formulations containing sanguinarine or chelerythrine or salts thereof or extracts containing them, in admixture with suitable carriers and/or excipients, for the treatment and/or the prevention of mucositis.

Sanguinarine or chelerythrine can be present in a substantially pure form or in the form of extracts of *Sanguinaria canadensis*, *Macleaya cordata* or *Macleaya macrocarpa*.

The invention further relates to the use of sanguinarine or chelerythrine or salts thereof or extracts containing them for the preparation of medicaments for the treatment and/or prevention of mucositis.

Furthermore it has been found, and this is a further object of the invention, that the salts of these alkaloids with luteic acid are particularly effective for the purposes of the present invention.

The salts of the invention are prepared by reaction of the alkaloids sulfates or chlorides with luteic acid sodium or potassium salt and subsequent crystallization.

Said salts, particularly the sanguinarine salt, exert antiphlogistic, analgesic, antiangiogenetic, antimicrobial, antifungal, cicatrising and antiproliferative action on both sensitive and resistant cells.

Luteic acid gives the alkaloid different bioavailability and increased antiviral activity, particularly against Citomegalovirus, Papillomavirus, Rhinovirus, Adenorinovirus, Herpes zoster and Herpes simplex; furthermore, luteic acid reduces bacterial and fungal adhesion to cells, thereby enhancing the antimicrobial and antifungal effect of the alkaloids.

This aspect is particularly advantageous in that mucositis is often associated with bacterial and/or fungal infections.

The formulations of the invention can further contain isobutylamides extracted from *Echinacea angustifolia* or synthesized from polyunsaturated acids, which have agonistic action on CB1 and CB2 cannabinoid receptors. Both natural and synthetic isobutylamides, when administered concomitantly with the radio-chemotherapeutic treatment, reduce the appearance of nausea and vomit which affect almost all of the treated patients, and this is a further particularly advantageous aspect of the invention.

The active principles contained in the formulations of the invention show negligible absorption through the oral route and can therefore be administered prophylactically, before the administration of the chemotherapeutic, or between chemotherapy cycles.

The compositions of the invention are able to reduce peripheral oncological pain already within 20 minutes; to prevent the formation of purulent plaques infected by saprophytes in the oral cavity, avoiding the use of antibiotics while reducing the progress of the infection; to reduce the

severity of the fungal infections and to contribute to restoration of mucus barriers.

The pharmaceutical compositions can be in the form of tablets, capsules or chewable tablets, chewing gums, creams, ointments, foams, vaginal
5 suppositories.

Tablets with slow dissolution in the oral cavity or chewable gums can be suited when the slow release of the active principles is desired.

According a preferred aspect, the formulations of the invention will further contain essential oils to increase the patient compliance in terms of
10 freshness of the oral cavity.

The effective dosages of sanguinarine and chelerythrine in the compositions of the invention can range from 1 to 20 mg, either in the free or salified form; the same alkaloids and the salts thereof can be solubilised in slow release gels consisting of proteoglycans or substituted celluloses. The
15 alkaloids can be incorporated in patches to be applied to the palate for the treatment of subjects with experience difficulty in using conventional formulations.

Suitable formulations for the treatment of mucositis of the digestive tract comprise tablets, capsules or dispersible granulates which promote
20 adhesion to the gastro-intestinal walls. For the treatment of mucositis of the genitourinary tract, particularly of the vagina, sanguinarine luteic acid salt, suitably formulated in vaginal suppositories, foams, gel and similar topical forms, proved particularly effective.

The compositions of the invention can be prepared according to
25 conventional, well known methods, such as those described in "Remington's Pharmaceutical Handbook", Mack Publishing Co., N.Y., USA, together with suitable excipients.

The examples reported hereinbelow illustrate the invention in greater

detail.

Example I - Preparation of sanguinarine luteic acid salt

3.68 g of sanguinarine chloride is dissolved in 100 ml of ethanol and added under stirring with 3.6 g of potassium luteate and the mixture is reacted
5 for 3 hours. The formed potassium chloride is filtered off and the solution is concentrated to small volume. 5.6 g of a salt having the following characteristics is obtained.

Example II - 1 Gram chewable tablets

	1. <i>Macleaya cordata</i> alkaloids (70%)	2.5 mg
10	2. Soy lecithin	30.0 mg
	3. Anhydrous citric acid	10.0 mg
	4. Lactose	240.0 mg
	5. Mannitol	550.0 mg
	6. Methylcellulose	40.0 mg
15	7. Palmitostearate	50.0 mg
	8. Berry flavours	40.0 mg
	9. Potassium acesulfame	0.5 mg
	10. Talc	10.0 mg

Example III - 1 Gram chewable tablets

20	1. Sanguinarine bisulfate	2.5 mg
	2. Soy lecithin	30.0 mg
	3. Anhydrous citric acid	10.0 mg
	4. Lactose	240.0 mg
	5. Mannitol	550.0 mg
25	6. Methylcellulose	40.0 mg
	7. Palmitostearate	50.0 mg
	8. Berry flavours	40.0 mg
	9. Potassium acesulfame	0.5 mg

	10. Talc	10.0 mg
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Example IV - 1 Gram chewable tablets

	1. Sanguinarine bisulfate	2.5 mg
	2. Soy lecithin	30.0 mg
5	3. Anhydrous citric acid	10.0 mg
	4. Lactose	240.0 mg
	5. Mannitol	550.0 mg
	6. Methylcellulose	40.0 mg
	7. Palmitostearate	50.0 mg
10	8. Berry flavours	40.0 mg
	9. Potassium acesulfame	0.5 mg
	10. Talc	10.0 mg

Example V - 1 Gram chewable tablets

	1. Sanguinarine luteicate	2.5 mg
15	2. Soy lecithin	30.0 mg
	3. Anhydrous citric acid	10.0 mg
	4. Lactose	240.0 mg
	5. Mannitol	550.0 mg
	6. Methylcellulose	40.0 mg
20	7. Palmitostearate	50.0 mg
	8. Berry flavours	40.0 mg
	9. Potassium acesulfame	0.5 mg
	10. Talc	10.0 mg

Example VI - Soft-gelatin capsules for the treatment of vaginal**25 mucositis**

	Sanguinarine luteicate	10 mg
	soy lecithin	50 mg
	beeswax	50 mg

vegetable oil q.s. to 800 mg

Example VII - Cream (oil in water emulsion) for inside and outside vaginal mucositis

	1. Sanguinarine bisulfate	200.0 mg
5	2. <i>Echinacea angustifolia</i> lipophilic extract	100.0 mg
	3. Propylene glycol	10.00 g
	4. Soy lecithin	50 mg
	5. Beeswax	50 mg
	6. Isopropyl myristate	5.00 g
10	7. Cetyl alcohol	5.00 g
	8. Polysorbate 80	3.00 g
	9. Carbomer	0.40 g
	10. Methyl para hydroxy benzoate	0.10 g
	11. Propyl para hydroxy benzoate	0.05 g
15	12. Purified water q.s. To	100 g

Example VIII - Vaginal suppository

	1. Sanguinarine bisulfate	3 mg
	2. Fatty acids glycerides q.s. to	2.0 g

CLAIMS

1. Formulations containing sanguinarine or chelerythrine or the salts thereof or extracts containing them in admixture with suitable carriers and/or
5 excipients for the treatment and/or prevention of mucositis.
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 extracts of *Sanguinaria canadensis*, *Macleaya cordata* or *Macleaya macrocarpa*.
- 10 5. Formulations as claimed in claim 1 wherein sanguinarine or chelerythrine are in the form of luteic acid salts.
6. Formulations as claimed in any one of claims 1 to 5 further containing natural or synthetic isobutylamides.
7. Formulations as claimed in claim 6 wherein isobutylamides are
15 contained in the *Echinacea angustifolia* lipophilic extract.
8. Formulations as claimed in any one of claims 1 to 7 in the form of tablets, granulates, capsules or chewable tablets, chewing gums, creams, ointments, foams, vaginal suppositories, patches.
9. Chelerythrine luteic acid salt.
- 20 10. Sanguinarine luteic acid salt.
11. The use of sanguinarine or chelerythrine or the salts thereof or extracts containing them for the preparation of medicaments for the treatment and/or prevention of mucositis.
12. The use as claimed in claim 11 wherein mucositis is induced by
25 chemotherapy, radiotherapy or immunosuppressive treatment.
13. The use as claimed in claim 11 or 12 wherein mucositis is buccal or vaginal mucositis.
14. The use as claimed in any one of claims 1 to 13 wherein sanguinarine or

chelerythrine are salified with luteic acid.

15. The use as claimed in any one of claims 12 to 14 in combination with natural or synthetic isobutylamides.