

COMPOSITIONS FOR THE TREATMENT OF DISORDERS OF THE UPPER RESPIRATORY TRACT AND INFLUENZA SYNDROMES

SUMMARY OF THE INVENTION

The present invention relates to compositions based on benzophenanthridine alkaloids, extract of *Hippophae rhamnoides* and extract of *Echinacea angustifolia*, which possess antibacterial, antiviral and anti-inflammatory activity and are useful in the treatment of bacterial and viral infections of the upper respiratory tract, and in the treatment of influenza.

Prior art

The preventive and curative treatment of influenza is an important target, because this illness affects millions of people all over the world every year, with a huge loss of working hours and serious complications which, in debilitated patients, elderly people and small children, can even be fatal.

Influenza is particularly dangerous in elderly patients because of its complications, especially if they already suffer from the respiratory disorders typical of old age. The same problem arises in infants, in whom influenza leaves an aftermath of continual colds and relapses. For many years, preventive vaccination was considered to be the most effective method of dealing with viral diseases. However, in the case of influenza, the efficacy of this measure is limited due the unusual antigen mutations caused by the appearance of new, resistant variants of the virus.

For this reason, chemotherapy and chemoprevention of viral infections are the gold standard today. Various products for the treatment of influenza exist, ranging from the old-fashioned adamantanes introduced in the 1960s to the recent neuraminidase inhibitors which, however, present low efficacy and often problems of toxicity, and cause the development of viral resistance. These substances have different impacts on strains A and B, so substances

which attack both strains are essential when the type of infection is not known *a priori*.

Flushing, inflammation and bacterial and/or fungal infection of the throat, with formation of plaques, are common symptoms that accompany
5 common influenza, colds and similar disorders. The common cold and influenza, which affect both children and adults up to three times a year on average, are mainly associated with viral infections, 40% of which are caused by rhinovirus, 10% by coronavirus, and a smaller proportion by adenovirus and parainfluenza virus. Although there is no specific treatment
10 for these disorders, antihistamines, decongestants and anti-inflammatories are considered useful because reduction of oedema alleviates pain and shortens the length of the disorder underlying the inflammation.

These disorders sometimes involve complications due to the onset of secondary bacterial infections, because the outlets of the nasal sinuses are
15 often obstructed by congestion of the mucous membranes where pathogenic germs can easily proliferate, causing fever and localised pain. In this case, antibiotic treatment is required in addition to symptomatic treatments.

The therapeutic aids used nowadays are based on eliminating possible complications, and are represented by antibiotics, anti-inflammatories and
20 antipyretics. However, not all the preparations currently available on the market can be used by children and pregnant women. Antibiotics, especially in infants, reduce the body's defences, leading to relapses. This means that antiviral preparations which are fairly harmless to both adult patients (including pregnant women) and children, and do not cause the development
25 of resistant viruses, is essential. The possibility of combining products which are perfectly tolerated and act on all fronts of a disorder is therefore required by the medical profession.

It has been reported in the literature that benzophenanthridine

alkaloids possess antimicrobial, antifungal, antiviral and antiangiogenetic activity. The most representative of these compounds is sanguinarine, which has mainly been used in the dental profession to date for its antibacterial and anti-inflammatory action, which is useful in inhibiting plaque and protecting the gums. Benzophenanthridine alkaloids are also characterised by an anti-inflammatory effect associated with a plurality of activities, performed at nanomolar concentrations, such as:

- inhibition of NFkB, a nuclear factor involved in inflammation and in the immune response to infections;
- 10 - antiangiogenetic activity: the angiogenesis process is involved in inflammation and depends on VEGF (vascular endothelial growth factor), whose effect has been demonstrated *in vitro* on the migration of HUVECs and *in vivo* on angiogenesis in different models. *In vitro*, sanguinarine markedly suppresses the inducement of cell migration, sprouting and cell survival to a dose-dependent extent;
- 15 - inhibition of 5- and 12-lipoxygenase.

These alkaloids perform a powerful synergistic action towards inflammatory processes and in bacterial and fungal infections, whereas their activity against viral infections is less marked. *Hippophae rhamnoides* extract possesses antiviral and mildly antibacterial properties.

DESCRIPTION OF THE INVENTION

The present invention relates to compositions based on:

- a) benzophenanthridine alkaloids;
- 25 b) extract of *Hippophae rhamnoides*;
- c) lipophilic extract of *Echinacea angustifolia*

having antibacterial, antiviral and anti-inflammatory activity, which are useful in the treatment of influenza and disorders of the upper respiratory

tract.

The compositions of the invention exert a strong antiviral activity on the most common strains of influenza viruses, together with an antibacterial action, which prevents the formation of bacterial plaques and infections of the upper respiratory tract which often result from influenza. The compositions according to the invention are particularly indicated for purulent otitis and mouth infections in general. Moreover, their anti-inflammatory action is useful to treat the fever and inflammation that normally accompany colds and influenza.

It has now surprisingly been found that the compositions of the invention possess an extremely powerful antiviral, antibacterial and anti-inflammatory activity, greater than that of the sum of the various components administered separately. Said effect may be due to a synergic action mechanism not foreseeable *a priori*, which takes place between the various components of the combination in question.

According to the invention, the compositions will contain the various components in the following intervals (by weight per unit dose):

- a) benzophenanthridine alkaloids: from 1 to 5;
- b) extract of *Hippophae rhamnoides*: from 10 to 100;
- c) lipophilic extract of *Echinacea angustifolia*: from 0.2 to 2.

According to a particularly preferred aspect, the compositions in question will contain the various components within the following intervals (by weight per unit dose):

- a) benzophenanthridine alkaloids: from 2 to 4;
- b) extract of *Hippophae rhamnoides*: from 15 to 45;
- c) lipophilic extract of *Echinacea angustifolia*: from 0.5 to 1.

According to a preferred aspect of the invention, the benzophenanthridine alkaloids will be selected from sanguinarine,

chelerythrine and chelidonine, or may be present in the form of extracts containing them, including their isomeric forms. Examples of said extracts are extracts of *Sanguinaria canadensis*, *Macleaya cordata* or *Macleaya microcarpa*, and *Chelidonium majus*. According to a particularly preferred aspect, the benzophenanthridine alkaloids will be present in the form of a purified extract of *Macleaya cordata* having an alkaloid titre of between 75 and 100%.

According to a preferred aspect, the benzophenanthridine alkaloids will be present in a form salified with luteic acid. Said salts, which are prepared by reacting the sulphates or chlorides of the alkaloids with the sodium or potassium salt of luteic acid and subsequent crystallisation, have proved particularly effective for the purposes of this invention.

According to a preferred aspect of this invention, the extract of *Hippophae rhamnoides* will be present as extract of *Hippophae rhamnoides* obtained by extraction from the aerial parts enriched with ellagic acid derivatives. According to a particularly preferred aspect, the extract of *Hippophae rhamnoides* will have an ellagitannin titre of 90%.

The extract of *Hippophae rhamnoides* is prepared by extraction from the aerial parts with alcohols having one to three carbon atoms, variously diluted with water, preferably with a 50% v/v mixture of ethanol/water, and then concentrating the water/ethanol extract until complete elimination of the organic solvent and adding to the resulting turbid suspension a quantity of polyvinylpyrrolidone amounting to 2% of the weight of the biomass. The clear solution obtained by filtration is absorbed on polystyrene resin, and the resin is washed until the soluble substances have been completely eliminated. The active ingredient that constitutes the extract used in the present invention is recovered by washing the resin with 90% ethanol, concentrating the ethanol eluate to a small volume and drying the residue under vacuum at a

temperature not exceeding 50°C.

Hippophae rhamnoides extract presents marked antiviral activity towards various strains of influenza A and B, and towards adenovirus, paramyxovirus, *Herpes catarrhalis* viruses, cytomegalovirus and respiratory syncytial virus. The extract also presents antibacterial activity, enhanced by the fact that the ellagic tannins complex the alkaloids, anchoring the complex with the residual hydrophilic part to the viral or bacterial proteins, thus preventing their multiplication and at the same time reducing the global toxicity of the combination.

10 *In vitro* tests have demonstrated that the compositions of the invention induce the production of interferon, and inhibit bacterial and fungal proliferation and the inflammatory and pain reaction.

According to a preferred aspect, the compositions of the invention will also contain essential oils of *Echinacea angustifolia*, or the isobutylamides contained in them, which possess a powerful anti-inflammatory and analgesic activity, as they are ligands of cannabinoids CB1 and CB2.

The compositions of the invention will be conveniently formulated in the form of tablets that dissolve slowly in the oral cavity or chewing gums that release the active components slowly, mouthwashes, gels for dispersal in the oral cavity, or the like. Said formulations can be prepared according to well-known conventional methods, such as those described in "Remington's Pharmaceutical Handbook", Mack Publishing Co., N.Y., USA, together with suitable excipients.

The invention will be illustrated in detail in the example below.

25 **Example** - 1000 mg chewable tablets containing

Extract of <i>Hippophae rhamnoides</i>	20 mg
Freeze-dried extract of <i>Echinacea angustifolia</i>	0.5 mg
Alcoholic extract of <i>Macleaya cordata</i>	2 mg

	Soya lecithin	30 mg
	Anhydrous citric acid	5 mg
	L-cysteine	5 mg
	Lactose	200 mg
5	Mannitol	567.5 mg
	Methylcellulose	40 mg
	Glycerol palmitostearate	50 mg
	Soft fruit flavourings	40 mg
	Potassium glycyrrhizinate	5 mg
10	Talc	10 mg
	Sodium bicarbonate	25 mg

CLAIMS

1. Compositions based on:
 - a) benzophenanthridine alkaloids;
 - 5 b) extract of *Hippophae rhamnoides*;
 - c) lipophilic extract of *Echinacea angustifolia*.
2. Compositions as claimed in claim 1, based on:
 - a) benzophenanthridine alkaloids selected from sanguinarine, chelerythrine and chelidonine;
 - 10 b) extract of *Hippophae rhamnoides* enriched with derivatives of ellagic acid;
 - c) lipophilic extract of *Echinacea angustifolia*.
3. Compositions as claimed in claims 1 and 2, wherein the various components are present in the following intervals (by weight per unit dose):
 - 15 a) benzophenanthridine alkaloids: from 1 to 5;
 - b) extract of *Hippophae rhamnoides*: from 10 to 100;
 - c) lipophilic extract of *Echinacea angustifolia*: from 0.2 to 2.
4. Compositions as claimed in the preceding claims, wherein the benzophenanthridine alkaloids sanguinarine, chelerythrine and chelidonine
20 are present in free or salified form, as such in substantially pure form or in the form of extracts of *Sanguinaria canadensis*, *Macleaya cordata* or *Macleaya microcarpa*, or *Chelidonium majus*.
5. Compositions as claimed in claim 4, wherein the benzophenanthridine alkaloids are present in salified form with luteic acid.
- 25 6. Compositions as claimed in claims 1-5, wherein the extract of *Hippophae rhamnoides* is present as extract of *Hippophae rhamnoides* obtained by extraction from the aerial parts enriched with ellagic acid derivatives.

7. Compositions as claimed in claim 6, wherein the extract of *Hippophae rhamnoides* has a 90% ellagitannin content.
8. Compositions as claimed in any one of claims 1 to 7, in the form of tablets that dissolve slowly in the oral cavity or chewing gums that release
5 the active ingredients slowly, mouthwashes, gels for dispersal in the oral cavity, or the like.
9. Compositions based on:
- a) benzophenanthridine alkaloids;
 - b) extract of *Hippophae rhamnoides*;
 - 10 c) lipophilic extract of *Echinacea angustifolia*
- for use in the treatment of bacterial and viral disorders of the upper respiratory tract.
10. Compositions for use according to, claim 9, wherein the bacterial and viral disorders of the upper respiratory tract are due to the sequelae of
15 infections caused by influenza viruses.