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(57) Abstract: Composition for the prevention and treatment of urinary tract infections containing, in combination, therapeutically effective quantities of cranberry (*Vaccinium macrocarpon*) and lactoferrin, for oral administration, in which the known antimicrobial action of cranberry is enhanced by a synergistic interaction with lactoferrin. The invention also concerns the use of cranberry and lactoferrin, in combination, for the production of a composition for the prevention and treatment of urinary tract infections, particularly indicated as a natural alternative to antibiotic therapy, or as a co-adjuvant in the said therapy, particularly in the prevention of recurrent urinary infections.



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**COMPOSITION CONTAINING CRANBERRY (VACCINIUM
MACROCARPON) AND LACTOFERRIN FOR THE PREVENTION AND
TREATMENT OF URINARY TRACT INFECTIONS**

5 The present invention concerns a composition containing cranberry (*Vaccinium macrocarpon*) and lactoferrin for the prevention and treatment of urinary tract infections (UTI). More specifically, the invention concerns a pharmaceutical or nutraceutical composition for oral administration indicated for the prevention and treatment of urinary tract infections, particularly in women,
10 both in the fertile period and during menopause, in which the known antimicrobial activity of cranberry is enhanced by synergic interaction with another active ingredient of natural origin – lactoferrin.

 As is known, urinary tract infections are characterised by the presence of bacteria in urine, in association with an inflammatory reaction in the host.
15 The bacteria responsible for urinary tract infections (often referred to, in the English language scientific literature, with the acronym UTI) are mainly gram-negative, and particularly *Escherichia coli*, which is the dominant uropathogen (from 75% to 95% of the cases). Much less frequent is *Staphylococcus saprophyticus* (from 5% to 20% of the cases); other enterobacteria such as *Klebsiella* and *Proteus* can only occasionally cause UTI (Susan A. Mehnert-Kay, Diagnosis and Management of Urinary Tract Infections, *Am. Fam. Physician*, 2005, **72**:451-6, 458).
20

 The onset of the infection is the result of interaction between the bacteria and the host's tissues. In particular, *E. coli* normally has type 1 fimbriae and P fimbriae, macromolecules of protein origin enabling the bacteria to
25 adhere to the uroepithelial cells.

 According to current knowledge, UTI affect over 40% of women of fertile age at least once. This category of women are actually the ones most at risk of contracting this type of pathology. UTI in women can be classified as:
30 acute uncomplicated cystitis, recurrent cystitis, uncomplicated acute pyelonephritis and complicated UTI. Urinary tract infections are also possible in men, but with much less incidence. Moreover, in both men and women, there

may occur cystitis correlated to catheter and asymptomatic bacteriuria, which is particularly found in the elderly (Bosisio, V. et al., A prospective, descriptive study on the practice and management of urinary tract infections by general practitioners in Italy: clinical pathways (Part II), *Arch. Ital. Urol. Androl.*, 2003, 5 75, 2).

Sexually active women have a high risk of contracting acute cystitis, which may also be due to lifestyle or to predisposition (such as having a short urethra). However, UTI are also frequent in women during menopause, due to a lowering of defences linked to vagina and urethra changes of a hormonal origin. The most typical symptoms are dysuria, an increase in the stimulus to urinate, and suprapubic pain. 10

Traditionally, the diagnosis of cystitis was based on urinoculture, considered positive in the case of isolation with a count above 100,000 colonies/ml. However, years of clinical practice and literature reviews have confirmed that acute cystitis may even arise with lower bacterial counts. 15

The treatment for acute cystitis envisages the use of trimethoprim-sulfamethoxazol as a first choice drug for three days, except in cases of allergy and in cases of patients affected by germs with a known *in-vitro* resistance due to recent antibiotic treatment, or resident in geographic areas with a drug-resistance above 10-20%. In these cases, the alternative is fluoroquinolones for three days (Susan A. Mehnert-Kay, *ibidem*; V. Bosisio, et al., *ibidem*). 20 Apart from the aforesaid cases, antibiotic treatment with fluoroquinolones is not recommended, however, as a first choice therapy in uncomplicated acute UTI, in order to preserve its effectiveness for complicated infections.

25 Cystitis can lead to persistent infections even after adequate antibiotic treatment (recurrent infections) or to a new onset of infection after microbiologically documented eradication (re-infections). Repeated infections caused by the same etiological agent are, by definition, complicated infections, and call for diagnostic examinations and more aggressive treatment plans. As 30 already noted, fluoroquinolones are particularly recommended in the treatment of complicated cystitis even if, in recent years, they have seen widespread use also in acute cystitis due to a problem of bacterial resistance. In this regard, it

has been reported (Karlowsky et al., Susceptibility of antimicrobial-resistant urinary *Escherichia coli* isolates to fluoroquinolones and nitrofurantoin, *Clin. Infect. Dis.*, 2003, **36**:183-7) that the resistance of *E. coli* to ampicillin is 38%, while it is 17% to trimethoprim-sulfamethoxazole, 0.8% to nitrofurantoin, and
5 from 1.9% to 2.5% to fluoroquinolones.

A comprehensive classification of UTIs, of the current diagnostic methods and of the respective possibilities of treatment with antibiotics was provided, in particular, by Orenstein and Wong (Orenstein, R., Wong E.S., Urinary tract infections in adults, *Am. Fam. Physician*, 1999, **59**:1225-
10 34,1237), in a publication in which for each specific pathological form an appropriate treatment is suggested, with a dosage and duration of treatment, as well as alternative treatments in case of contraindications or resistance.

Because of the problem of resistance to antibiotics, research has also been directed to alternative solutions for the prevention and treatment of cystitis, and particularly of uncomplicated acute cystitis. When the use of classic
15 antibiotic treatments does not achieve the desired results, or even in order to support and strengthen the action of these treatments, use is made of some vegetal active ingredients which have turned out to be beneficial in countering the most common inflammations in urinary tracts. Of these, one of the most
20 widespread is the cranberry (*Vaccinium macrocarpon*).

The cranberry or red berry (*Vaccinium macrocarpon*) is a bright red coloured berry of North American origin that grows exclusively in certain areas of the American continent, and particularly in the cool temperate regions of the USA (Massachusetts, New Jersey, Oregon, Washington, Wisconsin), and in
25 some areas of Canada and Chile. It differs from the bilberry (*Vaccinium myrtillus*), which is more common in Europe and has smaller bluish berries, with a qualitative and quantitative content of active ingredients and biological properties that are partly different.

The cranberry is grown on a large scale in the aforesaid regions of
30 North America, in sandy soil rich in water, and is harvested between May and October. Only 12% of the harvest is eaten as fresh fruit while the rest is sent to the food processing industry, where it is used in the form of juice for bever-

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ages and dried fruit for various processes as well as in the herbal field and in food supplements and nutraceutical preparations, where it is used in the form of syrups, concentrated juices, capsules of extract, tablets and powders.

Pure cranberry juice has a very acidic and astringent taste (pH $\approx$ 2,5) which many people do not find very agreeable. That is why, when used as a nutraceutical product, it is often employed in a cranberry "cocktail" consisting of at least 25% juice, sweetener, water and vitamin C.

Cranberry (*Vaccinium macrocarpon*) has been used as a urinary anti-septic for at least 200 years since even the native populations of North America knew its activity in preventing and treating infections and inflammations, particularly of the urinary tract. It has been used as a traditional treatment for UTI before the introduction of antibiotics, and continues to be widely used as a product for self-medication for this purpose.

The juice of berries, and particularly of cranberries, contains many organic compounds that can have the biological activity found in combating urinary infections. These compounds include benzoic acid (which is metabolised and eliminated in the form of hyppuric acid in urine), fructose, flavonoids, anthocyanosides, anthocyanidins and proanthocyanidins. The latter, in particular, have recently been found to have the antibacterial effect seen experimentally.

More specifically, in 1984 it was found that the most likely action mechanism through which cranberry juice performs its activity in the prevention of UTIs consists of inhibiting bacterial adherence (ascertained with strains deriving from clinical isolates of *E. coli*) to the epithelial cells of the urinary tract (Sobota A.E., Inhibition of bacterial adherence by cranberry juice: potential use for the treatment of urinary tract infections, *J. Urol.*, 1984, **131**:1013-6). Later, other *in-vitro* studies demonstrated an interference of cranberry juice in the adherence of other uropathogenic gram-negative strains besides *E. coli* (Schmidt D.R., Sobota A.E., An examination of the anti-adherence activity of cranberry juice on urinary and nonurinary bacterial isolates, *Microbios.*, 1988, **55**:173-181). Having found that the uropathogen strains rely on eukaryotic cells for the adherence of their type 1 and type P fimbriae in order to achieve

colonisation and the relative infection process, it was demonstrated that cranberry proanthocyanidins prevent the adherence of these fimbriae of the uropathogen strains of *E. coli* onto the cell membranes of the host cells.

Many clinical studies have shown the efficacy of the oral administration of cranberry in the treatment of UTI.

In the first relatively broad placebo-controlled study on the effectiveness of cranberry juice in the treatment of UTI, Avorn and co-workers (Avorn, J. et al., Reduction of bacteriuria and pyuria after ingestion of cranberry juice, *JAMA*, 1994, **271**:751-4) evaluated the effects of administering 300 ml/day (for 6 months) of a cranberry juice cocktail vs. placebo in 153 elderly women. At the end of the study, the pyuria and concentration of bacteria in urine was significantly reduced in the patients who had been treated with cranberry juice compared to those treated with placebo.

In a series of clinical trials conducted on a group of younger women, tablets of cranberry extract were used for the first time instead of the cranberry juice or cocktail, and this also achieved similar good results in terms of efficacy (Walker, E.B et al., Cranberry concentrate: UTI prophylaxis, *J. Fam. Pract.*, 1997, **45**:167-8). The US patent US 5,525,341, partly by the same authors (Walker et al.), concerns the preparation of a cranberry extract containing the biologically active fraction of this fruit that is responsible for inhibiting the bacterial adherence, but which also has, *inter alia*, a reduced acidity and lower sugar content compared to the raw juice.

Despite the large number of clinical trials reported in the literature on cranberry activity in the prevention and/or treatment of UTI, many of them do not appear sufficiently reliable in order to draw any hard and fast conclusion on the biological activity of cranberry *in vivo*. The first study considered to be of good quality on the topic was the one carried out by Kontiokari and co-workers in 2001 (Kontiokari T. et al., Randomised trial on cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women, *BMJ*, 2001, **322**:1571). This was a clinical trial carried out on 150 women divided into three groups treated for 12 months, respectively, with: 1) cranberry juice; 2) lactobacillus; 3) placebo. A statistically significant

reduction in the risk of UTI was found in 20% of the women treated with cranberry compared to the other two groups.

The second recent work considered sufficiently reliable on the therapeutic effects of cranberry (Stothers, L., A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women, *Can. J. Urol.*, 2002, **9**:1558-62) reports the results of a controlled and randomised clinical trial conducted on 150 women for a period longer than 12 months. This study also demonstrated the efficacy of administering cranberry both in the form of juice and tablets.

Even more recently, Di Martino and co-workers (Di Martino, P., et al., Reduction of *Escherichia coli* adherence to uroepithelial bladder cells after consumption of cranberry juice: a double-blind randomized placebo-controlled cross-over trial, *World J. Urol.* 2006, **24**:21-27) published the results of a double-blind randomised placebo-controlled cross-over trial on twenty healthy volunteers consisting of ten men and ten women. The analysis of the patients' urine enabled the *in-vivo* evaluation of the effectiveness of cranberry administration in inhibiting the adherence of *E. coli* to human uroepithelial cells.

In view of the above, it appears that cranberry administration for the treatment of urinary tract infections may carry out a valid co-adjuvant function in antibiotic chemoprophylaxis and could, in any case, be particularly significant in treating patients affected by recurrent UTI or those for whom prolonged antibiotic treatment is not recommended or possible.

In the light of the foregoing, it is evident that the natural antibiotic role of cranberry in the treatment of UTI is of great interest for subjects who intend to undergo non-pharmacological preventive treatment by taking products of natural origin in the long term especially in order to prevent the risk of recurrent infections or to eradicate persistent infections. It is thus evident the utility of a composition for oral administration having the characteristics of a safe natural therapy, devoid of the inconvenience and contraindications of antibiotics but nevertheless effective and rapidly active both in the prevention and treatment of UTIs, with an activity profile even higher than that of cranberry, especially in terms of speed of action.

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To this end, within the studies leading to the present invention, the possibility of combining cranberry with another active ingredient of natural origin having antibacterial properties – lactoferrin – was taken into consideration in order to produce a composition for oral administration that is particularly recommended in the prevention and treatment of UTIs.

As is known, lactoferrin is a multifunctional immunoregulatory glycoprotein of the transferrin family of proteins. It has a molecular weight of about 80 kDa and is normally found in the colostrum and milk of mammals (and particularly in human and bovine milk) and, to a lesser extent, in saliva, tears, bile, blood and gastric and genital mucosa secretions. Native lactoferrin is a glycosylated protein molecule having two main lobes each bonding with an atom of ferric ion (Fe^{3+}) in the presence of sodium bicarbonate. It is through this chelating activity of iron that lactoferrin performs its antibacterial (bacteriostatic) function, such as during breast-feeding, by reducing the availability of iron necessary for the growth and reproduction of pathogenic microorganisms.

The bacteriostatic and bactericide properties of lactoferrin were demonstrated *in vitro* for a number of pathogenic micro-organisms, both gram-positive and gram-negative ones, and have been used in order to prepare antibacterial compositions recommended for various specific infective pathologies.

In particular, European patent application EP-A-0753308 (Gambit International Ltd) proposes the topical use of lactoferrin in the treatment of acute or recurrent infections caused by *Streptococcus pyogenes*, *Staphylococcus aureus* or other gram+ intracellular pathogenic bacteria, with particular reference, but not exclusive, to the prevention and treatment of infections of the oropharyngeal tract. According to the aforesaid document, lactoferrin – administered in a topical preparation onto the affected area – exerts an anti-invasive action on the pathogenic micro-organisms, preventing their adherence to the walls of the host cells and their penetration inside. The proposed composition, which may also be associated with antibiotics, is preferably administered in the form of drops, chewing gum or powder for dermatological

application.

A more specific therapeutic indication for urinary and intestinal tract infections is described for lactoferrin in the international patent application WO 98/06425 (Holdingsbolaget Vid Göteborgs Universitet AB), which proposes
5 lactoferrin-based pharmaceutical compositions for oral administration in general for the prevention and treatment of infections, inflammations and even tumours, and specifically for the prevention and treatment of UTI and colitis. In this case, which is experimentally supported by *in-vitro* trials and in an animal model, possible associations with other active ingredients are not taken into
10 consideration.

Partly by the same authors of the preceding patent document is the publication of 2000 (Håversen L.A. et al., Human Lactoferrin and Peptides Derived from a Surface-Exposed Helical Region Reduce Experimental *Escherichia coli* Urinary Tract Infections in Mice, *Infection and Immunity*, Oct.
15 2000, **68**:5816-5823), in which lactoferrin was used in an animal model (mouse) of UTI. The results of the study showed a significant reduction in the infection and inflammation in mice with experimentally induced urinary infection after oral administration of lactoferrin.

Another field in which lactoferrin and its antibacterial activity have
20 been widely studied is that of infections by *Helicobacter pylori*, which affect the gastro-enteric tract and which are responsible, amongst other things, for gastric ulcer. According to patent application US 2002/0016289 (Conneely, O.M. et al.), lactoferrin was proposed in pharmaceutical compositions – possibly containing other active ingredients as one or more antibiotics – for the prevention and treatment of *H. pylori* infections. One of the most recent documents
25 clinically confirming the effectiveness of lactoferrin, via oral administration, in eradicating the gram-negative bacteria *Helicobacter pylori* is the publication by Di Mario and co-workers of a multicentre prospective study involving 402 patients. The study showed that administering lactoferrin for a period of seven
30 days can enhance the activity of antibiotics administered simultaneously (Di Mario, F. et al., Bovine lactoferrin for *Helicobacter pylori* eradication: an open, randomized, multicentre study, *Aliment. Pharmacol. Ther.*, 2006, **23**:1235-

1240).

Although the antibacterial properties of lactoferrin and cranberry, each considered separately, had been known in the literature, no-one had ever considered the possibility of combining their two active ingredients within a single composition for oral administration; nor had the property of synergic enhancement of the antibacterial activity of the two active ingredients ever been highlighted. It has now been found that an oral pharmaceutical form containing a cranberry-lactoferrin combination determines a conspicuous synergy of action, shown by its enhanced capacity to inhibit *E. coli* adherence to uroepithelial cells with respect to the activities shown by the individual components, and in the time required to obtain the desired effect compared to the longer times required by either cranberry or lactoferrin when used alone.

Hence, the present invention specifically provides a composition for the prevention and treatment of urinary tract infections that contains therapeutically effective quantities of cranberry (*Vaccinium macrocarpon*) and lactoferrin, in combination, in a physiologically acceptable vehicle. As already noted, the composition according to the present invention lends itself particularly well to oral administration, through which the active ingredients become, in any case, available in the site of action, presumably by passing through the urinary excretory pathway.

According to some preferred embodiments thereof, the proposed composition includes the following active components in the following proportions:

- cranberry

concentrated extract in powder	50 - 2000 mg
or	
pure juice	50 - 900 ml
- lactoferrin

	50 - 500 mg
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More preferably, each dosage unit of the proposed composition includes the following active components in the following proportions:

- cranberry

concentrated extract in powder	100 - 1000 mg
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- 10 -

or

pure juice

100 - 500 ml

▪ lactoferrin

100 - 200 mg

5 In a particularly preferred form, the composition according to the present invention consists of oral dosage units in which each dosage unit includes the following active components in the following proportions:

- cranberry, concentrated extract in powder 200 mg
- lactoferrin 100 mg

10 These dosage units can take the form of tablets, chewable tablets, soft or hard capsules, granules for drinkable solutions or drops for oral solutions, and are preferably made up of chewable tablets.

According to the pharmaceutical form and content of the active ingredients, the recommended dosage is one unit, 1 to 4 times a day. For the aforesaid preferred formulation, composed of 300 mg chewable tablets, the recommended dosage is 1 or 2 tablets per day.

15 The pharmaceutical or nutraceutical preparations according to the present invention can contain additives normally used in the pharmaceutical art such as sweeteners, flavourings, colorants, coatings and preservatives, inert diluents such as calcium carbonate, sodium carbonate, lactose and talc, binding agents such as starch, gelatine and polyvinylpyrrolidone, suspending agents such as methylcellulose or hydroxyethylcellulose, and imbibing agents such as lecithin, polyoxyethylene stearate and polyoxymethylene sorbitan monooleate, reducing agents such as ascorbic acid and its salts, as well as other suitable pharmaceutical excipients.

20 According to another aspect thereof, the present invention concerns the use of a combination of cranberry (*Vaccinium macrocarpon*) and lactoferrin for the production of a preparation for the prevention and treatment of urinary tract infections. The composition, which is specially designed for oral administration, comprises – as already noted – the following active components in the following proportions:

- cranberry concentrated extract in powder 50 - 2000 mg

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or

pure juice

50 - 900 ml

▪ lactoferrin

50 - 500 mg

Each dosage unit of the proposed composition for use in the treatment
 5 of UTIs – that can be presented in any one of the aforesaid pharmaceutical
 forms – preferably includes the following active components in the following
 proportions:

preferred

▪ cranberry

10 concentrated extract in powder 100 - 1000 mg 200 mg

or

pure juice

100 - 500 ml

▪ lactoferrin

100 - 200 mg

100 mg

More specifically, as can be seen from the above and from the ex-
 15 perimental data below, the cranberry and lactoferrin composition proposed
 according to the present invention is recommended for the prevention and
 treatment of acute and recurrent infections of the urinary tract, and even more
 specifically is recommended for the prevention of recurrent cystitis, since it
 can be taken for long periods and without the contraindications typical of anti-
 20 biotic chemoprophylaxis. Moreover, as already noted for cranberry not in
 combination, the preparations of natural origin proposed according to the
 present invention can also be used as co-adjuvants in connection with a suit-
 able antibiotic therapy.

The specific characteristics of the present invention, as well as its
 25 advantages and operative modalities, will be all the more evident with refer-
 ence to the detailed description presented below for mere exemplification
 purposes, along with the results of the experiments conducted on it and the
 comparative data regarding the prior art.

Biological trials on an animal model

30 To demonstrate the efficacy of the cranberry-lactoferrin association in
 inhibiting bacterial adherence, mice were used as the experimental animal
 model. The cranberry and lactoferrin-based products used were, respectively,

“100% Cranberry Powder” by NutriCran® Bio-100 of Wareham, MA, USA, and bovine lactoferrin “Lactoferrin High Grade, standard granulometry” by Biopole SA of Les Isnes, Belgium.

Materials and methods

5 **Bacteria** – Strains of *E. coli*, clinically isolated from patients with significant bacteriuria, were used. The bacteria were prepared for the adherence trial by means of centrifugation, washing in phosphate-buffered saline (PBS, pH 7.2) and suspension in a final concentration of 10^9 cells/ml.

10 **Epithelial cells** – The uroepithelial cells were obtained from the urinary sediment of women who did not have a medical record of UTI. The cells were collected via centrifugation and re-suspended in PBS buffer at a final concentration of 10^5 cells/ml.

Animals – Four groups of twenty mice each were used (each group consisting of 10 males and 10 females), and divided as follows:

- 15 • 20 mice receiving a diet consisting of feed added with just cranberry (20% of total weight of the feed).
- 20 mice receiving a diet consisting of feed added with just lactoferrin (10% of the total weight of the feed).
- 20 mice receiving a diet consisting of feed added with both cranberry (20% of total feed weight) and lactoferrin (10% of total feed weight).
- 20 • 20 mice, used as controls, receiving a normal diet (with no cranberry and lactoferrin added).

Method – Two days after and four days after feeding the animals with the feed enriched with the substances tested, the mice urine was collected in order to assess bacterial adherence to the uroepithelial cells.

25

 For this reason, the urine of five mice was pooled together, diluted 1:1 with distilled water and then used for the trial.

Bacterial adherence trial – Bacterial adherence was evaluated according to the technique described by Parsons and Schmidt (Parsons, C.L., Schmidt, J.D., In vitro bacterial adherence to vaginal cells of normal and cystitis-prone women, *J. Urol.*, 1980, **123**(2): 184-7). The urine of the mice treated with the tested substances was preventively incubated with *E. coli* (10^9 bacte-

30

ria) for 10 min. at 37°C. Then, the *E. coli* treated in this way and 10⁵ epithelial cells in PBS were mixed and incubated at 37°C for 30 minutes. The mixture was then filtered. The epithelial cells and bacteria adhering to them present on the filter were coloured with methylene blue and examined under a microscope. Adherence was evaluated as the average number of bacteria per epithelial cell (in a sample of 50 cells).

Results

The results of the experimentation, in terms of *E. coli* adherence to the uroepithelial cells after incubation with mouse urine, are reported in Table 1 below.

TABLE 1

E. coli adherence to uroepithelial cells after incubation with mouse urine

	After 2 days of treatment	After 4 days of treatment
	Number of bacteria per cell (mean $\pm$ s.e.)	
Urine of control mice (C)	28.3 $\pm$ 2.7	29.0 $\pm$ 2.9
Urine of mice treated with cranberry (I)	22.0 $\pm$ 2.3	19.0 $\pm$ 2.9
Urine of mice treated with lactoferrin (II)	24.0 $\pm$ 1.3	21.0 $\pm$ 2.3
Urine of mice treated with cranberry + lactoferrin (I+II)	13.0 $\pm$ 2.9	5.0 $\pm$ 2.3

Table 2, below, reports the statistical evaluation of the results reported in Table 1, with a calculation of the inhibition percentage.

TABLE 2

Statistical evaluation of the results and inhibition percentage

	After 2 days of treatment		After 4 days of treatment	
	p	% inhibition	p	% inhibition
I+II vs. C	<0.01	54.0%	<0.001	83.0%
I vs. C	<0.05	22.2%	<0.01	34.5%
II vs. C	n.s.*	15.2%	<0.05	27.6%

* not significant

5 As demonstrated by the aforesaid data, the cranberry-lactoferrin combination according to the present invention significantly inhibits bacterial adherence as early as the second day of treatment, and presents values above 80% inhibition after four days. The percentages of inhibition, both on the second and fourth day of treatment, are considerably higher than the values obtained with the sole use of either cranberry or lactoferrin.

10 Moreover, the combination is appreciably better as regards therapeutic efficacy – even better than what was expected by adding together the effectiveness of the two active ingredients.

15 The present invention has been disclosed with reference to some specific embodiments thereof, but it is to be understood that variations or modifications can be brought by persons skilled in the art without departing from the scope of the appended claims.

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CLAIMS

1. A composition for the prevention and treatment of urinary tract infections containing, in combination, therapeutically effective quantities of
 5 cranberry (*Vaccinium macrocarpon*) and lactoferrin, in a physiologically acceptable vehicle.

2. A composition according to claim 1, formulated as a composition for oral administration.

3. A composition according to claims 1 or 2, comprising the following
 10 active components in the following proportions:

- cranberry

concentrated extract in powder	50 - 2000 mg
or	
pure juice	50 - 900 ml
- 15 ▪ lactoferrin 50 - 500 mg

4. A composition according to claim 3, wherein each dosage unit comprises the following active components in the following proportions:

- cranberry

concentrated extract of powder	100 - 1000 mg
or	
pure juice	100 - 500 ml
- 20 ▪ lactoferrin 100 - 200 mg

5. A composition according to claim 4, wherein each dosage unit comprises the following active components in the following proportions:

- 25 ▪ cranberry, concentrated extract in powder 200 mg
- lactoferrin 100 mg

6. A composition according to any one of claims 2-5, presented in the form of tablets, chewable tablets, soft or hard capsules, granules for drinkable solutions or drops for oral solutions.

30 7. Use of a combination of cranberry (*Vaccinium macrocarpon*) and lactoferrin for the production of a composition for the prevention and treatment of urinary tract infections.

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8. Use according to claim 7, wherein the said composition is for oral administration.

9. Use according to claims 7 or 8, wherein the said composition includes the following active components in the following proportions:

- 5 ▪ cranberry
- concentrated extract in powder 50 - 2000 mg
- or
- pure juice 50 - 900 ml
- lactoferrin 50 - 500 mg

10 10. Use according to claim 9, wherein each dosage unit of the said composition includes the following active components in the following proportions:

- cranberry
- concentrated extract in powder 100 - 1000 mg
- 15 or
- pure juice 100 - 500 ml
- lactoferrin 100 - 200 mg

11. Use according to claim 10, wherein each of the said dosage units includes the following active components in the following proportions:

- 20 cranberry, concentrated extract in powder, 200 mg
- lactoferrin 100 mg

12. Use according to any one of claims 8-11, wherein the said composition is presented in the form of tablets, chewable tablets, soft or hard capsules, granules for drinkable solutions or drops for oral solutions.

25 13. Use according to any one of claims 7-12, wherein the said composition is indicated for the prevention and treatment of acute and recurrent urinary tract infections.

14. Use according to claim 13, wherein the said composition is indicated for the prevention of recurrent cystitis.