



(51) International Patent Classification:

A01N 37/06 (2006.01) A61K 8/34 (2006.01)
A01N 49/00 (2006.01) A61K 8/362 (2006.01)
A01N 31/04 (2006.01) A61L 2/18 (2006.01)
A01N 31/06 (2006.01) A01P 1/00 (2006.01)
A01N 27/00 (2006.01)

(21) International Application Number:

PCT/EP2019/062962

(22) International Filing Date:

20 May 2019 (20.05.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

18175856.6 04 June 2018 (04.06.2018) EP

(71) Applicant (for AE, AG, AU, BB, BH, BN, BW, BZ, CA, CY, EG, GB, GD, GH, GM, IE, IL, IN, JO, KE, KN, KW, LC, LK, LS, MT, MW, MY, NA, NG, NZ, OM, PG, QA, RW, SA, SC, SD, SG, SL, SZ, TT, TZ, UG, VC, ZA, ZM, ZW only): **UNILEVER PLC** [GB/GB]; a company registered in England and Wales under company no. 41424 of Unilever House, 100 Victoria Embankment, London Greater London EC4Y 0DY (GB).

(71) Applicant (for all designated States except AE, AG, AU, BB, BH, BN, BW, BZ, CA, CY, EG, GB, GD, GH, GM, IE, IL, IN, JO, KE, KN, KW, LC, LK, LS, MT, MW, MY, NA, NG, NZ, OM, PG, QA, RW, SA, SC, SD, SG, SL, SZ, TT, TZ, UG, US, VC, ZA, ZM, ZW): **UNILEVER N.V.** [NL/NL]; Weena 455, 3013 AL Rotterdam (NL).

(71) Applicant (for US only): **CONOPCO, INC., D/B/A UNILEVER** [US/US]; 700 Sylvan Avenue (A4), Englewood Cliffs, New Jersey 07632 (US).

(72) Inventors: **CAMPBELL-LEE, Stuart**; Unilever R&D Port Sunlight Quarry Road East, Bebington, Wirral Merseyside CH63 3JW (GB). **MITRA, Rupak**; Hindustan Unilever Ltd, Research Centre, 64, Main Road, Whitefield, Bangalore 560 066 (IN). **POINTON, Thomas, Richard**; Unilever R&D Port Sunlight Quarry Road East, Bebington, Wirral Merseyside CH63 3JW (GB). **STOTT, Ian, Peter**; Unilever R&D Port Sunlight Quarry Road East, Bebington, Wirral Merseyside CH63 3JW (GB).

(74) Agent: **CHISEM, Janet**; Unilever Patent Group Colworth House, Sharnbrook, Bedford Bedfordshire MK44 1LQ (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,

CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))

(54) Title: PRESERVATION COMPOSITIONS

(57) Abstract: A preservation system comprising: i) itaconic acid or salt thereof and ii) a secondary preservation chemical selected from the list consisting of terpineol, geraniol, perillyl alcohol, menthol, terpinene, linalool, citronellol and mixtures thereof.



PRESERVATION COMPOSITIONS

The present invention relates to preservation systems for use in consumer products.

Background

- 5 The consumer goods industry has a constant need for agents having antimicrobial properties, in particular for the preservation of products which are otherwise perishable (such as e.g. cosmetics, pharmaceutical products or foodstuffs).

A large number of antimicrobial active compounds are already employed as preservation chemicals, but alternatives that avoid possible ecological concerns and are readily tolerated
10 by the skin are required.

Such preservation systems should be stable, largely and preferably completely odourless, inexpensive to prepare, easy to formulate (i.e. preferably liquid) and should not be detrimental to the final product.

The present invention provides a particularly effective preservation system.

15 Description of the Invention

The present invention relates to an antimicrobial preservation system comprising:

- i. itaconic acid or salt thereof; and
- ii. a secondary preservation chemical selected from the list consisting of
20 terpineol, geraniol, perillyl alcohol, menthol, terpinene, linalool, citronellol and mixtures thereof.

A second aspect of the invention relates to a composition comprising the antimicrobial preserving system described above.

A third aspect of the invention relates to a method of preserving a composition comprising
25 the step of adding to the composition an antimicrobial preservation system comprising:

- i) itaconic acid or salt thereof; and
- ii) a secondary preservation chemical selected from the list consisting of terpineol,
geraniol, perillyl alcohol, menthol, terpinene, linalool, citronellol and mixtures thereof.

In one embodiment of method of the invention, compound i) and ii) are pre-mixed before
30 addition to the composition to be preserved.

In a second embodiment of method of the invention, compound i) and ii) are not pre-mixed before addition to the composition to be preserved.

Detailed Description of the Invention

5 The present invention relates to an antimicrobial preservation system comprising itaconic acid or salt thereof, preferably the acid.

The preservation system further comprises a secondary preservation chemical selected from the list consisting of terpineol, geraniol, perillyl alcohol, menthol, terpinene, linalool, citronellol.

10 Preferably the secondary preservation chemical is selected from the list consisting of terpineol, geraniol, perillyl alcohol, more preferably the secondary preservation chemical is terpineol.

It is preferred if the weight ratio of compound (C1 to C6), unsaturated, organic acid having at least two carboxyl groups, preferably itaconic acid i) to secondary preservation chemical ii) is from 1:50 to 50:1 more preferably from 1:10 to 10:1, most preferably from 1:5 to 5:1.

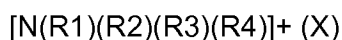
15 In a preferred embodiment of the invention the preserving system is included as part of a composition. Preferably the composition is a personal care composition and more preferably the composition is a hair treatment composition.

Preferably the total the level of preserving system within the composition is from 0.05 to 5 wt% of the total composition, more preferably from 0.2% to 2wt% of the total composition.

20 The compositions of the invention, comprising the preserving system of the invention, preferably comprise at least 75 wt %, preferably at least 80 wt %, more preferably at least 85 wt % and most preferably at least 87 wt % of water, by weight of the total composition.

It is preferred if the composition further comprises cationic, anionic, nonionic, zwitterionic or amphoteric surfactants or mixtures thereof.

25 Examples of suitable cationic surfactants which are useful include quaternary ammonium cationic surfactants corresponding to the following general formula:



30 in which R1, R2, R3, and R4 are each independently selected from (a) an aliphatic group of from 1 to 22 carbon atoms, or

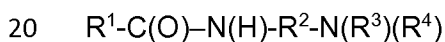
(b) an aromatic, alkoxy, polyoxyalkylene, alkylamido, hydroxyalkyl, aryl or alkylaryl group having up to 22 carbon atoms; and X is a salt-forming anion such as those selected from halide, (e.g. chloride, bromide), acetate, citrate, lactate, glycolate, phosphate nitrate, sulphate, and alkylsulphate radicals.

- 5 The aliphatic groups can contain, in addition to carbon and hydrogen atoms, ether linkages, and other groups such as amino groups. The longer chain aliphatic groups, e.g., those of about 12 carbons, or higher, can be saturated or unsaturated.

Specific examples of such preferred quaternary ammonium cationic surfactants are
10 cetyltrimethylammonium chloride (CTAC), behentrimonium chloride (BTAC) and mixtures thereof.

Alternatively, primary, secondary or tertiary fatty amines may be used in combination with an acid to provide a cationic surfactant suitable for use in the invention. The acid protonates the
15 amine and forms an amine salt *in situ*. The amine is therefore effectively a non-permanent quaternary ammonium or pseudo-quaternary ammonium cationic surfactant.

Suitable fatty amines of this type include amidoamines of the following general formula:



in which R^1 is a fatty acid chain containing from 12 to 22 carbon atoms, R^2 is an alkylene group containing from one to four carbon atoms, and R^3 and R^4 are each independently, an
25 alkyl group having from one to four carbon atoms. Particularly preferred is stearamidopropyldimethylamine.

Suitable anionic surfactants include the alkyl sulphates, alkyl ether sulphates, alkaryl sulphonates, alkanoyl isethionates, alkyl succinates, alkyl sulphosuccinates, N-alkoyl
30 sarcosinates, alkyl phosphates, alkyl ether phosphates, alkyl ether carboxylates, and alpha-olefin sulphonates, especially their sodium, magnesium ammonium and mono-, di- and triethanolamine salts. The alkyl and acyl groups generally contain from 8 to 18 carbon atoms and may be unsaturated. The alkyl ether sulphates, alkyl ether phosphates and alkyl ether carboxylates may contain from one to 10 ethylene oxide or propylene oxide units per molecule, and preferably contain 2 to 3 ethylene oxide units per molecule.

Examples of suitable anionic surfactants include sodium oleyl succinate, ammonium lauryl sulphosuccinate, ammonium lauryl sulphate, sodium dodecylbenzene sulphonate, triethanolamine dodecylbenzene sulphonate, sodium cocoyl isethionate, sodium lauroyl isethionate and sodium N-lauryl sarcosinate. The most preferred anionic surfactants are sodium lauryl sulphate, triethanolamine lauryl sulphate, triethanolamine monolauryl phosphate, sodium lauryl ether sulphate 1EO, 2EO and 3EO, ammonium lauryl sulphate and ammonium lauryl ether sulphate 1EO, 2EO and 3EO.

Nonionic surfactants suitable for use in compositions of the invention may include condensation products of aliphatic (C8-C18) primary or secondary linear or branched chain alcohols or phenols with alkylene oxides, usually ethylene oxide and generally having from 6 to 30 ethylene oxide groups. Other suitable nonionics include mono- or di-alkyl alkanolamides, glycolipids preferably selected from the group of rhamnolipids and sphorolipids.

Examples include coco mono- or di-ethanolamide and coco mono-isopropanolamide.

Amphoteric and zwitterionic surfactants suitable for use in compositions of the invention may include alkyl amine oxides, alkyl betaines, alkyl amidopropyl betaines, alkyl sulphobetaines (sultaines), alkyl glycinate, alkyl carboxyglycinate, alkyl amphopropionate, alkylamphoglycinate, alkyl amidopropyl hydroxysultaine, acyl taurates and acyl glutamates, wherein the alkyl and acyl groups have from 8 to 19 carbon atoms. Examples include lauryl amine oxide, cocodimethyl sulphopropyl betaine and preferably lauryl betaine, cocamidopropyl betaine and sodium cocamphopropionate.

Generally, the surfactants are present in shampoo compositions of the invention in an amount of from 0.1 to 50%, preferably from 5 to 30%, more preferably from 8% to 20% by weight.

The invention will now be illustrated by the following non-limiting Examples

Examples

The differing behaviours of inhibitory antimicrobials in isolation and mixtures have been widely explored using the concept of the Fractional Concentration and Fractional Inhibitory Concentration (FIC). See for instance JRW Lambert and R Lambert, J. Appl. Microbiol 95, 734 (2003); T. Jadavji, CG Prober and R Cheung, Antimicrobial Agents and Chemotherapy 26, 91 (1984), and WO 2004/006876. These parameters can be defined as follows:

FC (component a) = Concentration of component a tested in the mixture / MIC (component a tested as a single active)

FIC (component a) = MIC (component a tested in the mixture) / MIC (component a tested as a single active)

- 5 The interactions between antimicrobials can be additive, synergistic or possibly antagonistic depending on whether the efficacy of the combination is equivalent to, greater than or less than that obtained for the same total concentration of the individual components when tested alone.
- 10 These relationships can be expressed mathematically by summing the fractional MIC values for all the components present in the mixture to give the "fractional inhibitory index":

$$\sum \text{FIC} = \text{FIC}_{(\text{component 1})} + \text{FIC}_{(\text{component 2})}$$

- 15 Such that:

$\sum \text{FIC} \geq 1$ corresponds to additive or antagonistic activity

$\sum \text{FIC} < 1$ corresponds to synergistic activity

- 20 A comparable method is the calculation of the synergy index (SI) which is an industrial accepted method described by Kull, F.C.; Eisman, P.C.; Sylwestrowicz, H.D. and Mayer, R.L., in Applied Microbiology 9:538-541 (1961).

Methods

25

Liquid broth assays (MIC and checkerboard) were conducted to identify the minimum concentration(s) of individual and binary combinations of preservation chemicals. A modified methodology to ISO 20776-1:2006 was utilised for the screening as follows. Stock solutions of preservation chemicals and tryptic soy broth were inoculated with 1×10^6 microorganisms and incubated at 30°C for 24 hours, after which optical densities at OD_{600nm} were measured. MIC was defined as the concentration at which <25% growth was observed in comparison to a positive growth control containing no preservation chemicals. Preservation chemicals were screened at a concentration range of 0.0156-2%.

35

Table 1: Microorganism pools

Microorganism pool	
Pool 1	Gram negative non-fermenting bacteria: <i>Pseudomonas aeruginosa</i> , <i>Pseudomonas putida</i> & <i>Burkholderia cepacia</i>
Pool 2	Gram negative fermenting bacteria: <i>Enterobacter gergoviae</i> & <i>Klebsiella species</i>

5

Table 2: Chemical combination synergy scores

	Σ FIC synergy score			
	Itaconic acid		Citric Acid	
	Pool 1	Pool 2	Pool 1	Pool 2
Terpeniol	0.5	0.38	1	0.75
Geraniol	0.31	0.5	0.75	1.06
Perillyl alcohol	0.38	0.38	0.38	0.5

Claims

1. An antimicrobial preservation system comprising:
 - i) itaconic acid or salt thereof and
 - ii) a secondary preservation chemical selected from the list consisting of terpineol, geraniol, perillyl alcohol, menthol, terpinene, linalool, citronellol and mixtures thereof.
2. A preservation chemical according to claim 1 in which the secondary preservation chemical is selected from the list consisting of terpineol, geraniol, perillyl alcohol and mixtures thereof.
3. A preservation chemical according to any preceding claim in which the secondary preservation chemical is terpineol.
4. A preservation system according to any preceding claim in which the weight ratio of compound i) to compound ii) is from 1:50 to 50:1.
5. A preservation system according to any preceding claim in which the weight ratio of compound i) to compound ii) is from 1:10 to 10:1.
6. An aqueous composition comprising the preserving system according to any preceding claim.
7. A composition according to claim 6, which comprises at least 75 wt % water, by weight of the total composition.
8. A composition according to claim 6 or claim 7 in which the preserving system comprises from 0.05 to 5 wt% of the total composition.
9. A composition according to any one of claims 6 to 8 which is a personal care composition.
10. A composition according to claim 9 which is a hair treatment composition.

11. A method of preserving a composition comprising the step of adding to the composition an antimicrobial preservation system comprising:
- i) itaconic acid or salt thereof and
 - ii) a secondary preservation chemical selected from the group consisting of a terpeneol, geraniol, perillyl alcohol, menthol, terpinene, linalool, citronellol and mixtures thereof.
12. A method according to claim 11 in which compounds i) and ii) are pre-mixed before addition to the composition to be preserved.
13. A method according to claim 11 in which compounds i) and ii) are not pre-mixed before addition to the composition to be preserved.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/062962

A. CLASSIFICATION OF SUBJECT MATTER					
INV.	A01N37/06	A01N49/00	A01N31/04	A01N31/06	A01N27/00
	A61K8/34	A61K8/362	A61L2/18	A01P1/00	
ADD.					
According to International Patent Classification (IPC) or to both national classification and IPC					

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols) A01N A61K A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 105 296 995 A (TIANCHANG RUNDA METAL ANTIRUST AUXILIARY CO LTD) 3 February 2016 (2016-02-03) paragraph [0007] -----	1,4-8
X	FR 2 877 576 A1 (KADRI AHMED [FR]; BASRI FATIMA [FR]) 12 May 2006 (2006-05-12) page 4, lines 14-24 -----	1-9
Y	US 2014/311515 A1 (BARNE SAMEER KESHAV [IN] ET AL) 23 October 2014 (2014-10-23) paragraphs [0012] - [0017] -----	1-13
Y	US 2012/329874 A1 (PIVA ANDREA [IT] ET AL) 27 December 2012 (2012-12-27) paragraphs [0037], [0047], [0060] - [0065] -----	1-13
	-/--	

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 24 July 2019	Date of mailing of the international search report 02/08/2019
---	--

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Sawicki, Marcin
--	---

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/062962

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 9 326 924 B1 (FOURRE TARA [US] ET AL) 3 May 2016 (2016-05-03) columns 16-26; examples 1-3; tables 1-5, 7 -----	1-13
Y	CN 104 116 734 B (UNIV GUIZHOU) 18 May 2016 (2016-05-18) claim 1 -----	1-13
Y	JP 2018 048104 A (TAISHO PHARMA CO LTD) 29 March 2018 (2018-03-29) paragraph [0037]; example 10 -----	1-13
Y	US 2016/060660 A1 (HILLER KARSTEN [LU] ET AL) 3 March 2016 (2016-03-03) paragraphs [0176] - [0181]; example 6 -----	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2019/062962

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 105296995	A	03-02-2016	NONE
FR 2877576	A1	12-05-2006	NONE
US 2014311515	A1	23-10-2014	BR 112014009479 A2 09-05-2017 CN 103998011 A 20-08-2014 EA 201400535 A1 29-08-2014 EP 2773315 A2 10-09-2014 US 2014311515 A1 23-10-2014 WO 2013064360 A2 10-05-2013 ZA 201402431 B 27-01-2016
US 2012329874	A1	27-12-2012	BR PI0814769 A2 07-10-2014 BR 122017006341 B1 06-11-2018 CA 2695408 A1 12-02-2009 CA 2932088 A1 12-02-2009 DK 2185005 T3 18-12-2017 DK 2586319 T3 28-01-2019 EP 2185005 A2 19-05-2010 EP 2586319 A2 01-05-2013 ES 2653516 T3 07-02-2018 ES 2709050 T3 15-04-2019 HU E035487 T2 02-05-2018 KR 20100074118 A 01-07-2010 KR 20150006066 A 15-01-2015 KR 20160049550 A 09-05-2016 MX 355571 B 23-04-2018 PL 2185005 T3 30-03-2018 PL 2586319 T3 30-04-2019 PT 2185005 T 15-12-2017 RU 2010107601 A 10-09-2011 RU 2013111814 A 20-09-2014 RU 2017135245 A 09-04-2019 US 2011230560 A1 22-09-2011 US 2012329874 A1 27-12-2012 WO 2009019255 A2 12-02-2009
US 9326924	B1	03-05-2016	AU 2016222687 A1 24-08-2017 BR 112017018187 A2 17-04-2018 CA 2977351 A1 01-09-2016 CN 107257678 A 17-10-2017 EP 3261608 A1 03-01-2018 JP 2018506567 A 08-03-2018 RU 2017133244 A 28-03-2019 US 9326924 B1 03-05-2016 WO 2016138211 A1 01-09-2016
CN 104116734	B	18-05-2016	NONE
JP 2018048104	A	29-03-2018	JP 2018048104 A 29-03-2018 JP 2018162319 A 18-10-2018
US 2016060660	A1	03-03-2016	EP 2981610 A1 10-02-2016 US 2016060660 A1 03-03-2016 WO 2014161988 A1 09-10-2014