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(54) Title: COMPOSITIONS COMPRISING DEAD SEA EXTRACT AND AN EXTRACT OF HALOARCHAEA AND USES THEREOF

(57) Abstract: The present disclosure provides compositions comprising at least one Dead Sea extract and at least one extract of Haloarchaea, and uses thereof.

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COMPOSITIONS COMPRISING DEAD SEA EXTRACT AND AN EXTRACT OF HALOARCHAEA AND USES THEREOF

FIELD OF THE INVENTION

This invention relates to compositions comprising Dead Sea extract in combination with an extract of Haloarchaea, and their uses.

BACKGROUND OF THE INVENTION

Dead Sea water, salts, minerals and mud are well known for their therapeutic efficacy in treating a variety of skin conditions such as psoriasis, atopic dermatitis, acne and other inflammation skin diseases as well as for their cosmetic benefits **[1]-[5]**.

Haloarchaea (halophilic archaea, halophilic archaebacteria and halobacteria) are a class of the Euryarchaeota found in water saturated or nearly saturated with salt. A variety of Haloarchaea extracts and/or ingredients derived therefrom are known to have cosmetic and therapeutic properties **[6]-[10]**.

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Acknowledgement of the above references herein is not to be inferred as meaning that these are in any way relevant to the patentability of the presently disclosed subject matter.

SUMMARY OF THE INVENTION

The inventors of the present invention have developed an active combination of natural extract originated from the Dead Sea and an extract of Haloarchaea.

As the present application will further disclose, combinations comprising a Dead Sea extract and an extract of Haloarchaea have proven to have skin care and therapeutic attributes.

For example, combinations of the present invention have illustrated a synergistic behavior in reducing the gene expression of various genes that are related to collagen degradation. The combinations also significantly increased the activity of the extracellular enzyme Lysyl oxidase (LOX) which is known as an enzyme that catalyzes the formation of aldehydes from lysine residues in collagen and elastin precursors. These aldehydes created by LOX are highly reactive, resulting in cross-linking collagen, which is essential for stabilizing collagen fibrils.

The above observations illustrate a beneficial complementary opposite effect of the combinations of the present invention. The effect renders the combinations advantageous for collagen related functions.

Non-limiting advantageous attributes of the combinations of the present invention that may be associate with collagen function on the skin are skin firmness and/or elasticity. These attributes are advantageous *inter-alia* in terms of the ability of the combinations to inhibit age-related skin damage and to stimulate skin growth. Hence, the combinations of the present invention may be used as anti-aging active combinations, for example, in older population of the age of 60 years and above.

The effect of the combinations of the present invention has been studied also in connection with other biological pathways, apart from collagen degradation, that are *inter-alia* related to the skin. The results illustrated a different overall behavior of the

combinations compared to the individual ingredients comprising thereof (i.e., an extract from the Dead Sea and an extract of Haloarchaea).

The anti-inflammatory effect of the combinations of the present invention has been studied as well. The combinations illustrated a significant elevation in the level of hyaluronic acid in studied skin cells. Further, the combinations significantly reduced the level of Interleukin 1 beta (IL-1β) and Interleukin 6 (IL-6) in studied skin cells.

Thus, the present invention provides in one of its aspects a composition comprising at least one Dead Sea extract and at least one extract of Haloarchaea.

In another one of its aspects the present invention provides a composition comprising at least one Dead Sea extract and at least one extract of Haloarchaea, wherein said at least one Dead Sea extract is Dead Sea water (or a concentrate thereof), or an artificial aqueous solution having substantially the same salt and mineral content of the Dead Sea water (or a concentrate thereof), and wherein said at least one extract of Haloarchaea is an extract of Halobacterium *salinarum.*

In a further one of its aspects the present invention provides a composition comprising at least one Dead Sea extract and at least one extract of Halobacterium *salinarum*, wherein said at least one extract of Halobacterium *salinarum* being a fraction of said extract enriched with one or more of sulfated N-glycans (proteoglycans), lipids and squalene.

In yet a further one of its aspects the present invention provides a composition comprising at least one Dead Sea extract and at least one extract of Halobacterium *salinarum*, wherein said at least one extract of Halobacterium *salinarum* being a fraction of said extract enriched with one or more of sulfated N-glycans (proteoglycans), lipids and squalene, and wherein said fraction is obtainable (or obtained) by a process comprising fermentation of said Halobacterium *salinarum* in defined aqueous salt media at specific temperature and duration, said fermentation being followed by separation of the cells of said Halobacterium *salinarum* from the salt media and subsequent cell lysis by osmotic shock, followed by washing of the resulted lysate with water and concentrating thereof.

Yet, in a further one of its aspects the present invention provides a composition comprising at least one Dead Sea extract and at least one extract of Halobacterium *salinarum*, wherein said at least one extract of Halobacterium *salinarum* being a

Halobacterium Ferment Lysate Extract (the latter being the International Nomenclature Cosmetic Ingredient, INCI, of said extract).

In another one of its aspects the present invention provides a composition comprising an active combination of at least one Dead Sea extract and at least one extract of Haloarchaea, wherein said combination is a synergistic combination.

In a further one of its aspects the present invention provides skin-care composition/s (formulation/s) and/or pharmaceutical composition/s (formulation/s).

In yet a further one of its aspects the present invention provides a composition for use in the preparation of skin-care and/or pharmaceutical formulations.

Yet, in further one of its aspects the present invention provides a composition for use in one or more of protecting and/or improving the state of the skin, and preventing and/or treating imperfections of the skin of a subject.

In another one of its aspects the present invention provides a composition for use in one or more of protecting and/or improving the state of the skin, and preventing and/or treating imperfections of the skin of a subject, wherein said protecting and/or improving and/or preventing and/or treating are associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

In a further one of its aspects the present invention provides a composition for use in improving one or more of skin firmness and skin elasticity.

In a further one of its aspects the present invention provides a composition for use in a method of improving one or more of skin firmness and skin elasticity, wherein said method comprises topical application of said composition onto the skin of a subject.

In another one of its aspects the present invention provides a composition for use in improving one or more of skin firmness and skin elasticity, wherein said improving is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

In a further one of its aspects the present invention provides the use of a composition according to the invention for the preparation of a topical formulation (e.g., skin-care and/or pharmaceutical) wherein said topical formulation is for improving one or more of skin firmness and skin elasticity.

In a further one of its aspects the present invention provides the use of a composition according to the invention for the preparation of a topical formulation (e.g.,

skin-care and/or pharmaceutical) wherein said topical formulation is for improving one or more of skin firmness and skin elasticity, wherein said improving is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

In a further one of its aspects the present invention provides a method of improving one or more of skin firmness and skin elasticity, wherein said method comprises topical application of the composition according to the invention onto the skin of a subject.

In a further one of its aspects the present invention provides a method of improving one or more of skin firmness and skin elasticity, wherein said method comprises topical application of the composition according to the invention onto the skin of a subject, and wherein said improving is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

Yet, in a further one of its aspects the present invention provides a composition for use in treating and/or preventing at least one disease or disorder e.g., of the skin.

In another one of its aspects the present invention provides a composition for use in treating and/or preventing at least one disease or disorder of the skin, wherein said treating and/or preventing is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

In a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation (e.g., for the invented use/s as indicated herein above and below).

In yet a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation for one or more of treating and/or preventing a disease or disorder (e.g., of the skin); protecting and/or improving the state of the skin; and preventing and/or treating imperfections of the skin of a subject.

In a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation for one or more of

treating and/or preventing a disease or disorder (e.g., of the skin); protecting and/or improving the state of the skin; and preventing and/or treating imperfections of the skin of a subject, wherein one or more of the noted indications may be associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

In yet a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation for one or more of treating and/or preventing a disease or disorder (e.g., of the skin); protecting and/or improving the state of the skin; preventing and/or treating imperfections of the skin of a subject; and improving one or more of skin firmness and skin elasticity.

In yet a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation for one or more of treating and/or preventing a disease or disorder (e.g., of the skin); protecting and/or improving the state of the skin; preventing and/or treating imperfections of the skin of a subject; and improving one or more of skin firmness and skin elasticity, wherein one or more of the noted indications may be associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

Yet, in a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation for one or more of treating and/or preventing a disease or disorder (e.g., of the skin); protecting and/or improving the state of the skin; preventing and/or treating imperfections of the skin of a subject; inhibiting collagen degradation; increasing the activity of LOX; treating and/or preventing inflammation of the skin of a subject; improving one or more of skin firmness and skin elasticity; and enriching at least a region of a skin of a subject with hyaluronic acid.

In yet a further one of its aspects the present invention provides one or more of a lotion, an ointment, a gel, a mask, a toner, an essence, a shampoo, a moisturizer, a sunscreen, a cream, a stick, a spray, an aerosol, a foam, a paste, a mousse, a solid, semi-

solid, or a liquid make-up, a foundation, and an eye make-up comprising the composition according to the invention.

Yet, in a further one of its aspects the present invention provides a method for one or more of protecting and/or improving the state of the skin of a subject and preventing and/or treating imperfections of the skin of a subject in need thereof, wherein said method comprises topically administering the composition according to the invention onto the skin of the subject.

In another one of its aspects the present invention provides a method for one or more of protecting and/or improving the state of the skin of a subject and preventing and/or treating imperfections of the skin of a subject in need thereof, wherein said method comprises topically administering the composition according to the invention onto the skin of the subject, and wherein said protecting and/or improving and/or preventing and/or treating are associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

In a further one of its aspects the present invention provides a method for treating and/or preventing a disease or disorder of the skin of a subject, wherein said method comprises administering (by topical application) to a subject in need thereof a composition according to the invention.

In yet a further one of its aspects the present invention provides a method for treating and/or preventing a disease or disorder of the skin of a subject, wherein said method comprises administering (by topical application) to a subject in need thereof a composition according to the invention, and wherein said treating and/or preventing is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

Yet, in a further one of its aspects the present invention provides a method for one or more of inhibiting collagen degradation and increasing the activity of LOX, wherein said method comprises topically administering the composition according to the invention onto the skin of a subject.

In another one of its aspects the present invention provides a composition for use in a method for one or more of inhibiting collagen degradation and increasing the activity of LOX, wherein said method comprises topically administering the composition according to the invention onto the skin of a subject.

In yet a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation for one or more of inhibiting collagen degradation and increasing the activity of LOX.

Yet, in a further one of its aspects the present invention provides a method for inhibiting collagen degradation, wherein said method comprises topically administering the composition according to the invention onto the skin of a subject.

In another one of its aspects the present invention provides a composition for use in a method inhibiting collagen degradation, wherein said method comprises topically administering the composition according to the invention onto the skin of a subject.

In yet a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation for inhibiting collagen degradation.

In a further one of its aspects the present invention provides a method for increasing the activity of LOX, wherein said method comprises topically administering the composition according to the invention onto the skin of the subject, to thereby induce cross-linking of collagen and stabilize collagen fibrils.

In yet a further one of its aspects the present invention provides a composition for use in a method of increasing the activity of LOX, wherein said method comprises topically administering the composition according to the invention onto the skin of the subject, to thereby induce cross-linking of collagen and stabilize collagen fibrils.

In a further one of its aspects the present invention provides a method for stabilizing collagen fibrils, wherein said method comprises topically administering the composition according to the invention onto the skin of the subject, said administration increases the activity of LOX to induce cross-linking of collagen, thereby stabilizing collagen fibrils.

In yet a further one of its aspects the present invention provides a composition for use in a method for stabilizing collagen fibrils, wherein said method comprises topically administering the composition according to the invention onto the skin of the subject, said administration increases the activity of LOX to induce cross-linking of collagen, thereby stabilizing collagen fibrils.

Yet, in another one of its aspects the present invention provides a method for treating and/or preventing inflammation of the skin of a subject, wherein said method comprises topically administering to a subject in need thereof a composition according to the invention.

In another one of its aspects the present invention provides a method for treating and/or preventing inflammation of the skin of a subject, wherein said method comprises topically administering to a subject in need thereof a composition according to the invention, and wherein said treating and/or preventing is associated with reduction in one or more of IL-1β and IL-6 skin levels caused by said composition.

In another one of its aspects the present invention provides a composition for use in method for treating and/or preventing inflammation of the skin of a subject, wherein said method comprises topically administering to a subject in need thereof a composition according to the invention.

In a further one of its aspects the present invention provides a composition for use in a method for treating and/or preventing inflammation of the skin of a subject, wherein said method comprises topically administering to a subject in need thereof a composition according to the invention, and wherein said treating and/or preventing is associated with reduction in one or more of IL-1β and IL-6 skin levels caused by said composition.

In a further one of its aspects the present invention provides a composition according to the invention for use in a method of enriching at least a region of a skin of a subject with hyaluronic acid, wherein said method comprises application of said composition onto at least a region of a skin of the subject.

In yet a further one of its aspects the present invention provides a method of enriching a skin of a subject with hyaluronic acid, wherein said method comprises applying onto at least a region of a skin of said subject a composition according to the invention.

Yet, in a further one of its aspects the present invention provides the use of a composition according to the invention for the preparation of a topical formulation (e.g., skin-care and/or pharmaceutical) wherein said topical formulation is for enriching a skin cell with hyaluronic acid.

In a further one of its aspects the present invention provides the use of a composition according to the invention for the preparation of a topical formulation (e.g.,

skin-care and/or pharmaceutical) wherein said topical formulation is for stabilizing collagen fibrils.

In another one of its aspects the present invention provides the use of a composition according to the invention for the preparation of a topical formulation (e.g., skin-care and/or pharmaceutical) wherein said topical formulation is for stabilizing collagen fibrils, wherein the formulation increases the activity of LOX upon topical application to induce cross-linking of collagen, thereby stabilizing collagen fibrils.

In another one of its aspects the present invention provides a method for one or more of treating and/or preventing skin disease or disorder; protecting and/or improving the state of the skin; and preventing and/or treating imperfections of the skin, wherein said method comprises administration (e.g., topical) the composition according to the invention to a subject in need thereof, and wherein the disease and/or disorder and/or the state of the skin and/or the imperfections of the skin are associated with and/or are mediated by and/or are affected by and/or are related to the collagen degradation (WIKI) biological pathway.

In a further one of its aspects the present invention provides a composition according to the present invention for use in a method for one or more of treating and/or preventing skin disease or disorder; protecting and/or improving the state of the skin; and preventing and/or treating imperfections of the skin, wherein said method comprises administration (e.g., topical) said composition to a subject in need thereof, and wherein the disease and/or disorder and/or the state of the skin and/or the imperfections of the skin are associated with and/or are mediated by and/or are affected by and/or are related to the collagen degradation (WIKI) biological pathway.

Yet in a further one of its aspects the present invention provides the use of a composition according to the invention for the preparation of a topical formulation (e.g., skin-care and/or pharmaceutical) wherein said topical formulation is for one or more of treating and/or preventing skin disease or disorder; protecting and/or improving the state of the skin; and preventing and/or treating imperfections of the skin, and wherein the disease and/or disorder and/or the state of the skin and/or the imperfections of the skin are associated with and/or are mediated by and/or are affected by and/or are related to the collagen degradation (WIKI) biological pathway.

In a further one of its aspects the present invention provides a method for inhibiting collagen degradation, wherein said method comprises topically administering

the composition according to the invention onto the skin of a subject, wherein the composition comprises a synergistically active combination of at least one Dead Sea extract and at least one extract of Haloarchaea which synergistically reduces the expression of various genes that are related to the WIKI_COLLAGEN_DEGRADATION biological pathway, to thereby (synergistically) inhibit collagen degradation.

In another one of its aspects the present invention provides a composition for use in a method inhibiting collagen degradation, wherein said method comprises topically administering the composition according to the invention onto the skin of a subject, wherein the composition comprises a synergistically active combination of at least one Dead Sea extract and at least one extract of Haloarchaea which synergistically reduces the expression of various genes that are related to the WIKI_COLLAGEN_DEGRADATION biological pathway, to thereby (synergistically) inhibit collagen degradation.

In yet a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation for inhibiting collagen degradation, wherein the composition/formulation comprises a synergistically active combination of at least one Dead Sea extract and at least one extract of Haloarchaea which synergistically reduces the expression of various genes that are related to the WIKI_COLLAGEN_DEGRADATION biological pathway, to thereby (synergistically) inhibit collagen degradation.

In a further one of its aspects the present invention provides a method for one or more of skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity (anti dullness), the method comprising topical administration of the composition according to the invention onto the skin of a subject in need thereof.

In yet a further one of its aspects the present invention provides use of the composition of the invention in a method for one or more of skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity (anti dullness), wherein the method comprises topical administration of the composition according to the invention onto the skin of a subject in need thereof.

In yet a further one of its aspects the present invention provides the composition of the invention for use in a method for one or more of skin lifting and firming, restoring

skincare for women 60 years and above, and restoring luminosity (anti dullness), wherein the method comprises topical administration of the composition according to the invention onto the skin of a subject in need thereof.

Yet in a further one of its aspects the present invention provides the use of a composition according to the invention for the preparation of a topical formulation (e.g., skin-care and/or pharmaceutical) wherein said topical formulation is for one or more of skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity (anti dullness).

In a further one of its aspects the present invention provides a composition for use in improving one or more of skin firmness and skin elasticity, wherein the improving is associated with enhanced activity of LOX induced by the composition and/or with reduction in collagen degradation caused by the composition.

Yet, in a further one of its aspects the present invention provides a composition for use as disclosed herein and exemplified, wherein said composition comprises a synergistic active combination of at least one Dead Sea extract and at least one extract of Haloarchaea.

In further aspects the present invention provides a composition for use in, a composition for use in a method of, and use of the composition of the invention in the manufacture of a formulation (e.g., a pharmaceutical formulation and/or a skin care formulation) for, one or more of:

(i) protecting and/or improving the state of the skin, and preventing and/or treating imperfections of the skin of a subject; (ii) treating and/or preventing at least one disease or disorder e.g., treating and/or preventing inflammation of the skin of a subject;

(iii) improving one or more of skin firmness and skin elasticity;

(iv) inhibiting collagen degradation;

(v) increasing the activity of LOX;

(vi) enriching at least a region of a skin of a subject with hyaluronic acid;

(vii) stabilizing collagen fibrils; and

(viii) skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity (anti dullness).

One or more of the various methods and/or uses of the compositions as disclosed herein above and below (e.g., cosmetic and/or therapeutic) may be associate with one or

more of (i) enhanced skin activity of LOX; (ii) reduction in skin collagen degradation; (iii) enrichment of the skin with hyaluronic acid; (iv) reduction in skin IL-1β levels; and (v) reduction in skin IL-6 levels, induced/caused by the composition of the present invention.

One or more of the methods and/or the uses of the compositions as disclosed herein above and below may be associated with and/or mediated by and/or affected by and/or related to the collagen degradation biological pathway.

One or more of the therapeutic and/or cosmetic effects illustrated by the compositions of the invention may be associated with and/or mediated by and/or affected by and/or related to the collagen degradation biological pathway.

The present invention also provides compositions, extracts, uses and methods as herein defined and exemplified.

The methods and/or uses disclosed herein may be cosmetic methods or uses.

The methods and/or uses disclosed herein may be any one of therapeutic or non-therapeutic methods or uses.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to better understand the subject matter that is disclosed herein and to exemplify how it may be carried out in practice, embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Figure 1 represents an experimental diagram of a Human Dermal fibroblast (HDF) lysyl oxidase (LOX) activity assay, according to some embodiments of the invention.

Figure 2 represents lysyl oxidase results of HDF without stressor after 48 hours incubation, according to some embodiments of the invention.

Figure 3 represents lysyl oxidase results of HDF without stressor after 48 hours incubation, normalized to protein level (µg/µl), according to some embodiments of the invention.

Figure 4 represents an experimental diagram of a Human Dermal Fibroblast (HDF) and Hyaluronic Acid levels study, according to some embodiments of the invention.

Figure 5 represents Hyaluronic Acid level results, according to some embodiments of the invention.

Figure 6 represents an experimental diagram of a human HaCaT cell line study in a premature aging model, according to some embodiments of the invention.

Figure 7 represents Cytokine IL-1β level results, according to some embodiments of the invention.

Figure 8 represents Cytokine IL-6 level results, according to some embodiments of the invention.

Figure 9 illustrates the Heatmap, Arrays Clustered by logFC, observed in a DNA microarray assay, according to some embodiments of the invention.

Figure 10 illustrates a Heatmap showing all z-scores for 32 pathways selected from KEGG and wiki-pathways, observed in a DNA microarray assay, according to some embodiments of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides in one of its aspects a composition comprising (as an active combination) at least one Dead Sea extract and at least one extract of Haloarchaea.

Various embodiments will be detailed herein in connection with the composition of the invention. It is noted that one or more of these embodiments may be applicable to one or more aspects of the invention disclosed herein above and below e.g., uses of the composition of the invention and methods utilizing the composition of the invention.

As used herein, the expression "***active combination***" refers to the ability of the combination to exert a protective/preventive skin-care/therapeutic effect, as disclosed herein. Neither of the components is regarded as a carrier, diluent or excipient.

As used herein the term ***"Dead Sea extract***" refers to a mixture of natural materials obtained from the waters of the Dead Sea and/or the mud surrounding the Dead Sea and/or the soil bed of the Dead Sea.

In some embodiments the Dead Sea extract is a mixture of natural materials (e.g., salts, minerals) obtained from the waters of the Dead Sea.

In some embodiments the Dead Sea extract is Dead Sea water (herein abbreviated DSW) (or a concentrate thereof) or an aqueous solution having substantially the same salt and mineral content of the Dead Sea water (or a concentrate thereof).

In some embodiments, the Dead Sea extract is the Dead Sea water.

In some embodiments the "***Dead Sea water***" refers to the saline waters obtained from the Dead Sea (Israel or Jordan) region or an aqueous solution prepared by dissolving Dead Sea minerals and salts in an aqueous medium which simulate such natural solution, namely having substantially identical parameters characteristic of that measured for the natural DSW, said parameters being salts content/concentrations, minerals content/concentrations, cations and anions content/concentrations, ratio of divalent cations to monovalent cations, and optionally also one or more of TDS (Total Dissolved Salt, w/v), soluble natural substances, and other parameters known to define or characterize natural DSW.

In some embodiments, the Dead Sea extract is the Dead Sea water which may be obtained directly from the Dead Sea filtered water substantially having the same salt content (a hypersaline concentration) as that of the unfiltered Dead Sea water, or Dead Sea water treated by any one or more of various other methods employed to e.g., remove organic matter and residual contaminants therefrom.

It is noted that the Dead Sea water is not sea water from a sea different from the Dead Sea but it rather specific to the Dead Sea water that are reach with salts and minerals e.g., as disclosed herein.

It is further noted that the Dead Sea extract is not the artificial/synthetic sea water described in **[6]**.

In some embodiments, the Dead Sea extract is an artificial aqueous solution simulating the content of DSW i.e., having substantially identical content as that of DSW.

In some embodiments, the Dead Sea extract is an aqueous solution having substantially identical salts content, minerals content, salts concentration and mineral concentrations as that of DSW.

In some embodiments, the Dead Sea extract is an aqueous solution having substantially identical salts content, minerals content, salts concentration, minerals concentrations, concentration of a particular cation or anion, ratio of divalent cations to monovalent cations, TDS, soluble natural substances and other parameters known to define or characterize natural DSW.

In some embodiments, the Dead Sea extract is an aqueous solution simulating the salt content (a hypersaline concentration) of DSW i.e., having salt content substantially identical to that of DSW.

In some embodiments, the Dead Sea extract is an aqueous solution simulating the mineral content of DSW i.e., having mineral content substantially identical to that of DSW.

In some embodiments, the Dead Sea extract is an aqueous solution simulating the salt content (a hypersaline concentration) and the mineral content of DSW i.e., having salt content substantially identical to that of DSW, mineral content substantially identical to that of DSW and ratio of divalent cations to monovalent cations substantially identical to that of DSW.

In some embodiments, the Dead Sea water having:

1. a specific density of 1.25-1.35 g/ml,
2. pH = 4.6-5.6 (at 25°C), and/or
3. less than 100 cfu/g of non-pathogenic microbes.

The Dead Sea water having the above physical characteristics is a concentrated extract of Dead Sea water comprising (among other metal salt ions) Ca^{+2}, Mg^{+2}, Na^{+} and K^{+} and high concentrations of anions such as Cl^{-} and Br^{-}.

In some embodiments, the DSW is a clear colorless viscous liquid (at 25°C).

In some embodiments, the concentrations of these ions are, as assessed by a water analysis carried out by the Geological Survey of Israel:

Calcium (Ca^{+2}): 35,000-40,000 mg/L
Chloride (Cl^{-}): 320,000-370,000 mg/L
Magnesium (Mg^{+2}): 92,000-95,000 mg/L
Sodium (Na^{+}): 1800-3200 mg/L
Potassium (K^{+}): 2,500 mg/L, and
Bromide (Br^{-}): 10,000-12,000 mg/L.

Other minerals may also exist in the waters.

In some embodiments, the Dead Sea Water comprises:

Calcium (Ca^{+2}): 35,000-40,000 mg/L
Chloride (Cl^{-}): 320,000-370,000 mg/L
Magnesium (Mg^{+2}): 92,000-95,000 mg/L
Sodium (Na^{+}): 2400-3200 mg/L
Potassium (K^{+}): 2,500 mg/L, and
Bromide (Br^{-}): 10,000-12,000 mg/L.

Other minerals may also exist in the waters.

In some embodiments, the Dead Sea Water comprises:

Calcium (Ca^{+2}): 5,000-10,000 mg/L

Chloride (Cl^-): 315,000-360,000 mg/L

Magnesium (Mg^{+2}): 100,000-150,000 mg/L

Sodium (Na^+): 1800-2200 mg/L

Potassium (K^+): 1,000-2,000 mg/L, and

Bromide (Br^-): 5,000-10,000 mg/L.

Other minerals may also exist in the waters.

In some further embodiments, the Dead Sea Water comprises:

Calcium (Ca^{+2})	34,000 – 40,000 mg/L
Chloride (Cl^-)	320,000 – 370,000 mg/ L
Magnesium (Mg^{+2})	90,000 – 95,000 mg/L
Potassium (K^+)	1,300 – 2,200 mg/L
Sodium (Na^+)	1,500 – 2,800 mg/L
Bromide (Br^-)	11,000 – 15,000 mg/L.

Other minerals may also exist in the waters.

In some embodiments, the Dead Sea Water comprises:

Calcium (Ca^{+2}): 38,000 mg/L

Chloride (Cl^-): 345,000 mg/L

Magnesium (Mg^{+2}): 92,500 mg/L

Sodium (Na^+): 2000 mg/L

Strontium (Sr^{+2}): 800 mg/L

Potassium (K^+): 1,400 mg/L, and

Bromide (Br^-): 11,500 mg/L.

Other minerals may also exist in the waters.

In some embodiments, the Dead Sea Water comprises:

Calcium (Ca^{+2}): 38,000 mg/L

Chloride (Cl^-): 345,000 mg/L

Magnesium (Mg^{+2}): 92,500 mg/L

Sodium (Na^+): 2000 mg/L

Strontium (Sr^{+2}): 800 mg/L

Potassium (K^+): 1,400 mg/L, and

Bromide (Br^-): 11,500 mg/L.

Other minerals may also exist in the waters.

In some embodiments, the DSW is natural DSW which has undergone pre-treatment i.e., having been concentrated by allowing water to evaporate, for example through solar evaporation, thereafter reconstituted to afford a solution.

In some embodiments the Dead Sea extract is Dead Sea Water preparation commercially available as "***Maris Sal***" or "***Maris Aqua***" or "***Aqua, Maris Sal***" (AHAVA, Israel) referred to herein below also as "***Osmoter***".

The Osmoter is a concentrated Dead Sea water that has a high concentration of salts e.g., magnesium, calcium, strontium, bromine, boron and lithium which are characteristic Dead Sea minerals. The Osmoter has high ratio of divalent cations, mainly magnesium and calcium vs. monovalent cations, mainly potassium and sodium.

In some embodiments the ratio between the magnesium and calcium divalent cations to the potassium and sodium monovalent cations in the Osmoter is [92,500mg/l+38,000mg/l]/[1400mg/l+2000mg/l]=130,500/3400=38.38.

In some embodiments, the Osmoter is the product: Geological Survey - Ministry of National Infrastructures, State of Israel, especially for AHAVA-Dead Sea Laboratories (CAS# INCI Monograph ID:11089), also known as Dead Sea Works LTD.

In some embodiments, the Osmoter comprises the following ions: Mg^{+2} (92,500 mg/L), Ca^{+2} (38,000 mg/L), K^{+} (1,400 mg/L), Na^{+} (2,000 mg/L), Sr^{+2} (800 mg/L), Cl^{-} (345,000 mg/L) and Br^{-} (11,500 mg/L). Other minerals may also exist in the Osmoter.

In some embodiments, the Osmoter has the following composition:

Salt normality (N)		Salt normality (N)	
Na	0.118 (2.720 g/l)	Rb	3.5×10^{-6} ($<3 \times 10^{-4}$ g/l)
K	0.054 (2.100 g/l)	Sb	$<1.6 \times 10^{-7}$ ($<2 \times 10^{-5}$ g/l)
Ca	0.873 (35.000 g/l)	Sr	7.6×10^{-3} (0.670 g/l)
Mg	3.815 (92.700 g/l)	V	$<7.9 \times 10^{-5}$ (<0.004 g/l)
Ba	6.6×10^{-5} (0.009 g/l)	Th	$<8.6 \times 10^{-8}$ ($<2 \times 10^{-5}$ g/l)
Cd	$<1.8 \times 10^{-7}$ ($<2 \times 10^{-5}$ g/l)	U	$<8.4 \times 10^{-8}$ ($<2 \times 10^{-5}$ g/l)
Co	$<3.4 \times 10^{-5}$ (<0.002 g/l)	Zn	$<3.06 \times 10^{-5}$ (<0.002 g/l)
Cu	$<3.15 \times 10^{-5}$ (<0.004 g/l)		
Cr	$<3.85 \times 10^{-4}$ (<0.02 g/l)	Cl	9.75 (346 g/l)
Fe	$<3.58 \times 10^{-5}$ (<0.002 g/l)	Br	0.175 (14 g/l)
Li	5.76×10^{-3} (0.040 g/l)	B	0.011 (0.120 g/l)

Mn	1.82×10^{-4} (0.010 g/l)	As	2.7×10^{-5} (0.002 g/l)
Mo	$<1.04 \times 10^{-6}$ ($<10^{-4}$ g/l)	I	6.30×10^{-7} (8×10^{-8} g/l)
Ni	$<3.4 \times 10^{-5}$ (<0.002 g/l)	SiO2	$<3.33 \times 10^{-4}$ (<0.02 g/l)
Pb	$<9.6 \times 10^{-8}$ ($<2 \times 10^{-5}$)	SiO4	$<2.2 \times 10^{-3}$ (<0.2 g/l)

In some embodiments the ratio between the magnesium and calcium divalent cations to the potassium and sodium monovalent cations in the Dead Sea extract e.g., Dead Sea water, is between about 20 to about 55. At time it is about 20.0, 21.0, 22.0, 23.0, 24.0, 25.0, 26.0, 27.0, 28.0, 29.0, 30.0, 31.0, 32.0, 33.0, 34.0, 35.0, 36.0, 37.0, 38.0, 39.0, 40.0, 41.0, 42.0, 43.0, 44.0, 45.0, 46.0, 47.0, 48.0, 49.0, 50.0, 51.0, 52.0, 53.0, 54.0 and about 55.0. In some embodiments said ratio is about 23.7, at times about 25.9, at times about 27.0, at times about 29.5, at times about 38.1, at times about 38.4, at times about 40.0, at time about 44.0, even at times about 53.6. Any value which is between any one of the above values is within the scope of the present disclosure.

In some embodiments the Dead Sea extract is Dead Sea mud.

In some embodiments the Dead Sea extract is typically an active fraction having by itself at least one attribute which may be enhanced in a combination with the at least one extract of Haloarchaea.

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is at least about 0.01% (w/w). At time it is about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%. 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%. 0.18%, 0.19%, 0.20%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%. 0.28%, 0.29%, 0.30%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%. 0.38%, 0.39%, 0.40%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%. 0.48%, 0.49%, 0.50%, 0.51%, 0.52%, 0.53%, 0.54%, 0.55%, 0.56%, 0.57%. 0.58%, 0.59%, 0.60%, 0.61%, 0.62%, 0.63%, 0.64%, 0.65%, 0.66%, 0.67%. 0.68%, 0.69%, 0.70%, 0.71%, 0.72%, 0.73%, 0.74%, 0.75%, 0.76%, 0.77%. 0.78%, 0.79%, 0.80%, 0.81%, 0.82%, 0.83%, 0.84%, 0.85%, 0.86%, 0.87%. 0.88%, 0.89%, 0.90%, 0.91%, 0.92%, 0.93%, 0.94%, 0.95%, 0.96%, 0.97%. 0.98%, 0.99%, 1.00%, 1.10%, 1.10%, 1.11%, 1.12%, 1.13%, 1.14%, 1.15%, 1.16%, 1.17%. 1.18%, 1.19%, 1.20%, 1.21%, 1.22%, 1.23%, 1.24%, 1.25%, 1.26%, 1.27%. 1.28%, 1.29%, 1.30%, 1.31%, 1.32%, 1.33%, 1.34%, 1.35%, 1.36%, 1.37%. 1.38%, 1.39%, 1.40%, 1.41%, 1.42%, 1.43%, 1.44%, 1.45%, 1.46%, 1.47%. 1.48%, 1.49%, 1.50%, 1.51%, 1.52%, 1.53%, 1.54%, 1.55%, 1.56%, 1.57%. 1.58%, 1.59%, 1.60%,

1.61%, 1.62%, 1.63%, 1.64%, 1.65%, 1.66%, 1.67%. 1.68%, 1.69%, 1.70%, 1.71%, 1.72%, 1.73%, 1.74%, 1.75%, 1.76%, 1.77%. 1.78%, 1.79%, 1.80%, 1.81%, 1.82%, 1.83%, 1.84%, 1.85%, 1.86%, 1.87%. 1.88%, 1.89%, 1.90%, 1.91%, 1.92%, 1.93%, 1.94%, 1.95%, 1.96%, 1.97%. 1.98%, 1.99%, 2.00%, 2.10%, 2.11%, 2.12%, 2.13%, 2.14%, 2.15%, 2.16%, 2.17%. 2.18%, 2.19%, 2.20%, 2.21%, 2.22%, 2.23%, 2.24%, 2.25%, 2.26%, 2.27%. 2.28%, 2.29%, 2.30%, 2.31%, 2.32%, 2.33%, 2.34%, 2.35%, 2.36%, 2.37%. 2.38%, 2.39%, 2.40%, 2.41%, 2.42%, 2.43%, 2.44%, 2.45%, 2.46%, 2.47%. 2.48%, 2.49% and about 2.50% (w/w). Any value which is between any one of the above values is within the scope of the present disclosure.

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is at between about 0.01% to about 2.40% (w/w), at times between about 0.01% to about 2.00% (w/w), at times between about 0.01% to about 1.50% (w/w), at times between about 0.01% to about 1.00% (w/w), at times between about 0.05% to about 2.40% (w/w), at times between about 0.05% to about 2.00% (w/w), at times between about 0.05% to about 1.50% (w/w), at times between about 0.05% to about 1.00% (w/w), at times between about 0.10% to about 2.40% (w/w), at times between about 0.10% to about 2.00% (w/w), at times between about 0.10% to about 1.50% (w/w), at times between about 0.10% to about 1.00% (w/w), at times between about 0.20% to about 2.40% (w/w), at times between about 0.20% to about 2.00% (w/w), at times between about 0.20% to about 1.50% (w/w), at times between about 0.20% to about 1.00% (w/w), at times between about 0.30% to about 2.40% (w/w), at times between about 0.30% to about 2.00% (w/w), at times between about 0.30% to about 1.50% (w/w), at times between about 0.30% to about 1.00% (w/w), at times between about 0.40% to about 2.40% (w/w), at times between about 0.40% to about 2.00% (w/w), at times between about 0.40% to about 1.50% (w/w), at times between about 0.40% to about 1.00% (w/w), inclusive the end points values.

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is at between about 0.5% to about 2.40% (w/w), at times between about 0.5% to about 2.00% (w/w), at times between about 0.5% to about 1.50% (w/w), at times between about 0.5% to about 1.00% (w/w, inclusive the end points values.

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is at least about 0.1% (w/w) inclusive.

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is at least about 0.2% (w/w) inclusive.

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is at least about 0.3% (w/w) inclusive.

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is at least about 0.4% (w/w) inclusive.

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is at least about 0.5% (w/w) inclusive.

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 0.1 % (w/w).

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 0.2 % (w/w).

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 0.3 % (w/w).

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 0.4 % (w/w).

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 0.5 % (w/w).

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 0.6 % (w/w).

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 0.7 % (w/w).

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 0.8 % (w/w).

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 0.9 % (w/w).

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 1.0 % (w/w).

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 2.0 % (w/w).

The term "***Haloarchaea extract***" or any lingual variations thereof relates to a fraction obtained from Haloarchaea. The term "***Haloarchaea***" may be interchangeable with the terms "***Halophilic Archaea***", "***Halophilic Archaebacteria***" and "***Halobacteria***".

The Haloarchaea extract may be obtained according to known procedures. Various extracts of Haloarchaea are also commercially available.

In some embodiments the Haloarchaea extract is a resulted product of a controlled fermentation of Haloarchaea followed by lysis (e.g., lysis by osmosis).

In some embodiments the Haloarchaea extract is obtainable by a controlled fermentation of Haloarchaea followed by lysis (e.g., lysis by osmosis).

In some embodiments the Haloarchaea extract is an aqueous extract.

In some embodiments the Haloarchaea extract is an aqueous extract substantially free of an organic solvent e.g., one or more of a halogenated solvent (e.g., dichloromethane) and a C_1-C_4 alkanol (e.g., ethanol).

In some embodiments the Haloarchaea extract is an aqueous extract free of an organic solvent e.g., one or more of a halogenated solvent (e.g., dichloromethane) and a C_1-C_4 alkanol (e.g., ethanol).

In some embodiments the Haloarchaea extract is of a liquid form.

In some embodiments the Haloarchaea extract further comprises at least one stabilizer.

In some embodiments the Haloarchaea extract is soluble in water.

In some embodiments the Haloarchaea extract is soluble in a polar solvent.

In some embodiments the Haloarchaea extract is soluble in 10% ethanol.

In some embodiments the Haloarchaea extract is obtainable by extraction of the Haloarchaea in a polar solvent e.g., water.

In some embodiments the polar solvent is not an organic solvent.

In some embodiments the polar solvent is not a halogenated solvent and/or a C_1-C_4 alkanol.

In some embodiments the polar solvent is not a halogenated solvent e.g., dichloromethane.

In some embodiments the polar solvent is not a C_1-C_4 alkanol e.g., ethanol.

In some embodiments the Haloarchaea extract is an oil extract.

In some embodiments the Haloarchaea extract is not an oil extract.

In some embodiments the Haloarchaea extract is provided in an oil form.

In some embodiments the Haloarchaea extract is not provided in an oil form.

In some embodiments the Haloarchaea extract is Halobacterium *salinarum* extract.

In some embodiments the Halobacterium *salinarum* extract is a fraction enriched with one or more of sulfated N-glycans (proteoglycans), lipids and squalene.

In some embodiments the Halobacterium *salinarum* extract is a fraction enriched with an aqueous mixture of sulfated N-glycans (proteoglycans), lipids and squalene.

In some embodiments the Halobacterium *salinarum* extract is a fraction enriched with one or more sulfated N-glycans (proteoglycans), e.g., 0.1-0.5 ppm.

In some embodiments the Halobacterium *salinarum* extract is a fraction enriched with one or more lipids.

In some embodiments the Halobacterium *salinarum* extract is a fraction enriched with squalene.

In some embodiments the Halobacterium *salinarum* extract is a resulted product of Halobacterium *salinarum* fermentation and lysis.

In some embodiments the Halobacterium *salinarum* extract is obtainable (or obtained) by Halobacterium *salinarum* fermentation followed by lysis.

In some embodiments the Halobacterium *salinarum* extract is obtainable (or obtained) by a process comprising:

(a) fermentation of the Halobacterium *salinarum* in a defined aqueous salt media at specific temperature and duration;

(b) separation of the cells of the Halobacterium *salinarum* from the salt media;

(c) lysis of the separated cell by osmotic shock;

(d) washing of the resulted lysate with water; and

(e) concentrating the lysate.

In some embodiments the process may further comprise sterilization.

In some embodiments the process may further comprise stabilization of the extract.

In some embodiments the Halobacterium *salinarum* extract is produced by Applied Biotechnologies (product reference No. HC001), *See* **[10]** (the content of which is incorporated herein by reference).

In some embodiments the Halobacterium *salinarum* extract is Halobacterium Ferment Lysate Extract (INCI).

In some embodiments the Halobacterium extract e.g., *salinarum* extract may be formulated with at least one additive such as a stabilizer, a diluent, a carrier, a filler, an antioxidant or any other inert additive/s.

In some embodiments the Halobacterium *salinarum* extract may be formulated along with a predetermined amount of at least one additive such as a stabilizer, a diluent, a carrier, a filler, an antioxidant or any other inert additive/s.

In some embodiments the additive may be a non-natural additive.

In some embodiments the additive may be a natural additive.

In some embodiments the Halobacterium *salinarum* extract further comprises at least one stabilizer.

In some embodiments the stabilizer may be a non-natural stabilizer.

In some embodiments the stabilizer may be a natural stabilizer.

In some embodiments the Halobacterium *salinarum* extract is an extract stabilized with 1% PRESA-FERM i.e., LACTOCOCCUS FERMENT EXTRACT (INCI) 0.35%, and LACTOBACILLUS/ BRASSICA NIGRA SEED FERMENT EXTRACT (INCI) 0.65%.

In some embodiments the Halobacterium *salinarum* extract is produced by a controlled fermentation of Haloarchaea followed by lysis of the cells. In particular, by the following process: culture by fermentation of Halobacterium *salinarum* (inocula of Halobacterium salinarum, wildtype) in a bioreactor. Extraction by osmo-lysis with water and sterilization by tyndallisation at 90°C (three times for 30 min). The extract is subsequently stabilized against microbial growth with PRESA-FERM.

In some embodiments the Halobacterium *salinarum* is a wildtype Halobacterium *salinarum*.

In some embodiments the Haloarchaea extract is as herein described and exemplified.

The Haloarchaea extract is typically an active fraction having by itself at least one attribute which may be enhanced in a combination with the Dead Sea extract.

Without wishing to be bound by theory, in the combinations of the present invention, apart from being by itself an active ingredient, the at least one Haloarchaea extract may serve as an adjuvant and/or a booster of the at least one Dead Sea extract, improving/enhancing at least one therapeutic and/or cosmetic activities illustrated by the Dead Sea extract.

Without wishing to be bound by theory, in the combinations of the present invention, apart from being by itself an active ingredient, the at least one Dead Sea extract may serve as an adjuvant and/or a booster of the at least one Haloarchaea extract, improving/enhancing at least one therapeutic and/or cosmetic activities illustrated by the Haloarchaea extract.

In some embodiments the at least one Dead Sea extract may boost the activity of at least one biomaterial from the Haloarchaea extract.

In some embodiments the at least one Haloarchaea extract may boost the activity of at least one material from the Dead Sea extract.

In some embodiments the Halobacterium *salinarum* extract is a fraction enriched with squalene e.g., a triterpene with skin moisturizing attributes e.g., resulting with skin luminous (anti dullness). In some embodiments, the at least one Dead Sea extract of the combinations of the present invention may boost this attribute.

In some embodiments the Halobacterium *salinarum* extract is a fraction enriched with sulfated N-glycans (proteoglycans). Sulfated proteoglycans derived from Haloarchaea are known as having the ability to penetrate to a larger extent into the skin than corresponding hyaluronic acid. Such an activity may be boosted by the at least one Dead Sea extract of the combinations of the present invention.

In some embodiments the Halobacterium *salinarum* extract is a fraction enriched with lipids which activity (e.g., antioxidation) may be boosted by the at least one Dead Sea extract of the combinations of the present invention.

Non limiting examples of attributes that are related to the Halobacterium *salinarum* extract Halobacterium Ferment Lysate Extract (INCI) which may be boosted in the combinations of the present invention by the at least one Dead Sea extract are one or more of: maintains skin elasticity by protecting the structure relevant protein Elastin; protect skin lipids from oxidative damage by natural antioxidants; counteract ageing-dependent loss of Glycosaminoglycans of skin by natural proteoglycans; stimulating fibroblast growth; metallo-protease inhibition (anti-inflammatory); protecting fibroblasts

against UVB radiation; antioxidative protection (through sulfated polysaccharides and the natural lipid protector squalene); regenerate the skin by rebalancing sulfated glycosaminoglycans (GAG) in the connective tissue preventing typical signs of mature and stressed skin; counteract inflammatory processes (e.g., by inhibiting proinflammatory protease-enzymes); and improve skin elasticity resulting in smoother out lines and reduced wrinkles.

In some embodiments the composition of the invention comprises at least one Dead Sea extract and at least one extract of Haloarchaea, wherein said at least one Dead Sea extract is Dead Sea water (or a concentrate thereof), or an artificial aqueous solution having substantially the same salt and mineral content of the Dead Sea water (or a concentrate thereof), and wherein said at least one extract of Haloarchaea is an extract of Halobacterium *salinarum.*

In some embodiments the composition of the invention comprises at least one Dead Sea extract and at least one extract of Halobacterium *salinarum*, wherein said at least one extract of Halobacterium *salinarum* being a fraction of said extract enriched with one or more of sulfated N-glycans (proteoglycans), lipids and squalene.

In some embodiments the composition of the invention comprises at least one Dead Sea extract and at least one extract of Halobacterium *salinarum*, wherein said at least one extract of Halobacterium *salinarum* being a fraction of said extract enriched with one or more of sulfated N-glycans (proteoglycans), lipids and squalene, and wherein said fraction is obtainable (or obtained) by a process comprising fermentation of said Halobacterium *salinarum* in defined aqueous salt media at specific temperature and duration, said fermentation being followed by separation of the cells of said Halobacterium *salinarum* from the salt media and subsequent cell lysis by osmotic shock, followed by washing of the resulted lysate with water and concentrating thereof.

In some embodiments the composition of the invention comprises at least one Dead Sea extract and at least one extract of Halobacterium *salinarum*, wherein said at least one extract of Halobacterium *salinarum* being a Halobacterium Ferment Lysate Extract (the latter being the International Nomenclature Cosmetic Ingredient, INCI, of said extract).

In some embodiments the composition of the invention is a synergistic composition.

Thus, in another one of its aspects the present invention provides a composition for use as disclosed herein and exemplified, wherein said composition comprises a synergistic active combination of at least one Dead Sea extract and at least one extract of Haloarchaea.

In some embodiments the Haloarchaea extract is different from that described in **[6]**. In particular, the extract is not one obtained by bursting of the wall of the plasma membrane of the Haloarchaea by ultrasound technique.

In some embodiments the Haloarchaea extract is different from that described in **[7]**. In particular, the extract is not one obtained by utilizing extraction in organic solvents i.e., halogenated solvent such as dichloromethane and C_1-C_4 alkanol such as ethanol.

In some embodiments the Haloarchaea extract is different from that described in **[8]**. In particular, the extract is not one obtained by the method described therein. In some embodiments the Haloarchaea extract is not an extract of Halobacterium *salinarum* VKPM V-11850 that is described in **[8]**.

In some embodiments the Haloarchaea extract is different from that described in **[9]**. In particular, the extract is not one obtained by the method described therein. In some embodiments the Haloarchaea extract is not an extract of Archaebacteria DN-1 that is described in **[9]**.

In some embodiments the Haloarchaea extract is different from any one of those described in **[6]**, **[7]**, **[8]** and **[9]**.

In some embodiments the composition of the invention is devoid of an extract of the Apple of Sodom (AoS) (*Calotropis Procera*).

In some embodiments the composition of the invention is devoid of an extract of the *Dunaliella* alga.

In some embodiments the composition of the invention is devoid of an extract of the Apple of Sodom (AoS) (*Calotropis Procera*) and of an extract of the *Dunaliella* alga.

In some embodiments the composition of the invention is not for treating radiation damaged skin.

In some embodiments the composition of the invention is not for treating tumors e.g., skin tumors.

In some embodiments the composition of the invention is not for treating radiation damaged skin and tumors e.g., skin tumors.

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is at least about 0.10% (w/w). At time it is about 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%. 0.18%, 0.19%, 0.20%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%. 0.28%, 0.29%, 0.30%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%. 0.38%, 0.39%, 0.40%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%. 0.48%, 0.49%, 0.50%, 0.51%, 0.52%, 0.53%, 0.54%, 0.55%, 0.56%, 0.57%. 0.58%, 0.59%, 0.60%, 0.61%, 0.62%, 0.63%, 0.64%, 0.65%, 0.66%, 0.67%. 0.68%, 0.69%, 0.70%, 0.71%, 0.72%, 0.73%, 0.74%, 0.75%, 0.76%, 0.77%. 0.78%, 0.79%, 0.80%, 0.81%, 0.82%, 0.83%, 0.84%, 0.85%, 0.86%, 0.87%. 0.88%, 0.89%, 0.90%, 0.91%, 0.92%, 0.93%, 0.94%, 0.95%, 0.96%, 0.97%. 0.98%, 0.99%, 1.00%, 1.10%, 1.10%, 1.11%, 1.12%, 1.13%, 1.14%, 1.15%, 1.16%, 1.17%. 1.18%, 1.19%, 1.20%, 1.21%, 1.22%, 1.23%, 1.24%, 1.25%, 1.26%, 1.27%. 1.28%, 1.29%, 1.30%, 1.31%, 1.32%, 1.33%, 1.34%, 1.35%, 1.36%, 1.37%. 1.38%, 1.39%, 1.40%, 1.41%, 1.42%, 1.43%, 1.44%, 1.45%, 1.46%, 1.47%. 1.48%, 1.49%, 1.50%, 1.51%, 1.52%, 1.53%, 1.54%, 1.55%, 1.56%, 1.57%. 1.58%, 1.59%, 1.60%, 1.61%, 1.62%, 1.63%, 1.64%, 1.65%, 1.66%, 1.67%. 1.68%, 1.69%, 1.70%, 1.71%, 1.72%, 1.73%, 1.74%, 1.75%, 1.76%, 1.77%. 1.78%, 1.79%, 1.80%, 1.81%, 1.82%, 1.83%, 1.84%, 1.85%, 1.86%, 1.87%. 1.88%, 1.89%, 1.90%, 1.91%, 1.92%, 1.93%, 1.94%, 1.95%, 1.96%, 1.97%. 1.98%, 1.99% and about 2.00% (w/w). Any value which is between any one of the above values is within the scope of the present disclosure.

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is at between about 0.10% to about 2.00% (w/w), at times between about 0.10% to about 1.50% (w/w), at times between about 0.10% to about 1.00% (w/w), at times between about 0.2% to about 2.00% (w/w), at times between about 0.2% to about 1.50% (w/w), at times between about 0.2% to about 1.00% (w/w), at times between about 0.30% to about 2.00% (w/w), at times between about 0.30% to about 1.50% (w/w), at times between about 0.30% to about 1.00% (w/w), at times between about 0.40% to about 2.00% (w/w), at times between about 0.40% to about 1.50% (w/w), at times between about 0.40% to about 1.00% (w/w), at times between about 0.50% to about 2.00% (w/w), at times between about 0.50% to about 1.50% (w/w), at times between about 0.50% to about 1.00% (w/w), inclusive the end points values.

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is at least about 0.10 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is at least about 0.20 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is at least about 0.30 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is at least about 0.40 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is at least about 0.50 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 0.10 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 0.20 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 0.30 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 0.40 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 0.50 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 0.60 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 0.70 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 0.80 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 0.90 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1.00 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1.10 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1.20 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1.30 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1.40 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1.50 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1.60 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1.70 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1.80 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1.90 % (w/w).

In some embodiments the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 2.00 % (w/w).

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is at between about 0.5% to about 2.40% (w/w), at times between about 0.5% to about 2.00% (w/w), at times between about 0.5% to about 1.50% (w/w), at times between about 0.5% to about 1.00% (w/w, inclusive the end points values, and the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is at between about 0.5% to about 2.00% (w/w), at times at between about 1.00% to about 2.00% (w/w) inclusive the end points values.

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is at least about 0.5% (w/w) inclusive and the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is at least about 0.5% (w/w), inclusive.

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is at least about 0.5% (w/w) inclusive and the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is at least about 1.00% (w/w), inclusive.

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is at between about 0.5% to about 2.00% (w/w) and the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is at between about 0.5% to about 2.00% (w/w), inclusive the end points values.

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 0.5% (w/w) and the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 0.5% (w/w).

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 0.5% (w/w) and the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1.0% (w/w).

In some embodiments the concentration of the Dead Sea extract (e.g., Dead Sea water) in the composition (or formulation) of the invention is about 0.5% (w/w) and the concentration of the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 2.0% (w/w).

In some embodiments the ratio between the Dead Sea extract (e.g., Dead Sea water) and the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is selected from 1:1, 1:2, 1:3 or 1:4.

In some embodiments the ratio between the Dead Sea extract (e.g., Dead Sea water) and the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is between about 1:1 to about 1:4, inclusive.

In some embodiments the ratio between the Dead Sea extract (e.g., Dead Sea water) and the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1:1.

In some embodiments the ratio between the Dead Sea extract (e.g., Dead Sea water) and the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1:2.

In some embodiments the ratio between the Dead Sea extract (e.g., Dead Sea water) and the Haloarchaea extract (e.g., Halobacterium *salinarum* extract) in the composition (or formulation) of the invention is about 1:4.

In some embodiments, the composition of the invention is a cosmetic composition.

In some embodiments, the composition of the invention is a pharmaceutical composition.

In some embodiments, the composition of the invention e.g., pharmaceutical or cosmetic composition, is for topical application.

In some embodiments, the composition of the invention is an anti-aging composition e.g., inhibiting and/or preventing and/or treating age-related skin damage/s, the composition comprises an anti-aging active combination of at least one Dead Sea extract and at least one extract of Haloarchaea.

In some embodiments, the composition is a synergistic composition.

In some embodiments, the composition is a synergistic composition, comprising an active synergistic combination of at least one Dead Sea extract and at least one extract of Haloarchaea.

The compositions of the present invention may be made into a wide variety of product forms suitable for, e.g., topical administration onto the skin of a subject. Non-limiting examples are a lotion, an ointment, a gel, a mask, a toner, an essence, a shampoo, a moisturizer, a sunscreen, a cream, a stick, a spray, an aerosol, a foam, a paste, a mousse and a variety of cosmetics or skin-care formulations including solid, semi-solid, or a liquid make-up such as foundations, eye make-up, etc.

In some embodiments the liquid may be applied onto the skin as a moisturizer.

In some embodiments, the composition of the invention is formulated as a lotion.

In some embodiments, the composition of the invention is formulated as an emulsion.

In some embodiments, the composition of the invention is formulated as a facial formulation.

In some embodiments, the composition of the invention is formulated as a body formulation.

In some embodiments, the composition of the invention is formulated as a leave on formulation.

In some embodiments, the composition of the invention is formulated as a rinse off formulation.

As used herein, a "***leave on***" (in contrary to "***rinse off***") composition/formulation refers to a composition/formulation that may be in prolonged contact with the skin and can be applied to a skin region without the need to remove it from the skin (e.g., by wiping or rinsing it off) in any way.

In some embodiments, the leave-on composition/formulation may be adapted to be applied to a skin region and to be left on the skin for a time sufficient to achieve an end result.

The viscosity of the composition according to the invention may vary depending on the form (e.g., lotion, cream, etc.), concentration of the active combination, the carrier, the purpose (e.g., cosmetic or therapeutic), end user and other parameters.

The compositions according to the invention (cosmetic or therapeutic) may comprise at least one dermatological, cosmetically or pharmaceutically acceptable additive selected amongst inert and effect-inducing additives. Such additives are necessary for example for storage purposes, stability of the formulation, texture of the formulation for topical application and the like.

In some embodiments, the inert additive is selected from a diluent, a preservative, an abrasive, an anti-caking agent, an antistatic agent, a binder, a buffer, a dispersant, an emollient, an emulsifier, a co-emulsifiers, a fibrous material, a film forming agent, a fixative, a foaming agent, a foam stabilizer, a foam booster, a gallant, a lubricant, a moisture barrier agent, an opacifier (e.g., styrene/acrylamide copolymer), a plasticizer, a preservative, a propellant, a stabilizer, a surfactant, a suspending agent, a thickener, a wetting agent, and a liquefier.

In some embodiments, the at least one inert additive is a smoothness enhancer ingredient, such as silica.

In some embodiments, the at least one inert additive is a skin delivery agent.

In some embodiments, the at least one inert additive is of an encapsulated form e.g., protected from oxidation.

In some embodiments, the at least one inert additive is an antioxidant (e.g., Vitamin C) in an encapsulated form.

In some embodiments, the at least one inert additive is a chelator (e.g., synthetic EDTA) that stabilizes the composition/formulation (e.g., the presence thereof avoid redox/oxidation of one or more ingredients of the composition/formulation).

In the compositions of the present invention the one or more additives (e.g., dermatological, cosmetically or pharmaceutically acceptable additive) complete the content of the composition to 100% (w/w). In some embodiments the total cumulative content of such additives, at times including water, is at least about 95.6% (w/w).

In some embodiments the additive may be a non-natural additive.

In some embodiments the additive may be a natural additive.

Further non limiting additives that may form part of the compositions of the present invention are one or more of: a solvent, an emulsion stabilizer, an emulsifier, a

skin/hair conditioning agent, an emollient, a humectant, a surfactant, a preservative, a film forming agent, anti-static agent, viscosity controlling agent, chelator, suspending agent and an antioxidant.

In some embodiments one or more of the additives of the invention may be synthetic or natural (e.g., from a plant/vegetable).

In some embodiments the composition of the present invention comprises at least one additive, preferably being a non-natural additive.

In some embodiments the composition of the present invention comprises at least one additive, preferably being a synthetic additive.

In some embodiments the composition of the present invention comprises at least one stabilizer, which may be natural, non-natural or a combination thereof.

In some embodiments, each of the at least one dermatological, cosmetically or pharmaceutically acceptable additives may constitute between about 0.05 to 15% of the total weight of the formulation. In some embodiments, the at least one additive constitutes between 0.05% and 10% or between 0.05% and 8%, or between 0.05% and 7%, or between 0.05% and 6%, or between 0.05% and 5% of the total weight of the formulation.

In some embodiments, the at least one inert additive is a diluent being selected from water, Bisabolol, propane diol, propylene glycol, butylene glycol, glycerin, safflower oil and mixtures thereof.

In some embodiments, the at least one inert additive is a preservative being selected from one or more of methylparaben, methyldibromo glutaronitrile, phenethyl alcohol, glyceryl caprilate, propylparaben, methylisothiazolinone, decylene glycol, dehydroacetic acid, phenoxyethanol, benzoic acid, 2-methyl-2H-isothiazoline-3-one, polyethylene glycol monococoate, polyethylene glycol dicocoate, polyethylene Glycol, iodopropynyl butylcarbamate, 1.2-hexanediol, caprylyl glycol, imidazolidinyl urea, DMDM Hydantoin, Ipbc, MIT, 2,3-bronopol.

In some embodiments, the at least one inert additive is a synthetic preservative necessary for preserving the formulations of the invention for long storage and/or use purposes.

In further embodiments, the inert additive is an emulsifier being selected from one or more of cetyl hydroxyethylcellulose, cetyl alcohol, ceteth-20 (a polyethylene glycol derivative of cetyl alcohol), cetearyl olivate, cetyl palmitate, sorbitan olivate, sorbitan

palmitate, stearates, steareth-20 (polyethylene glycol ethers of stearic acid- octadecyl polyoxyethylene ether), and steareth-25.

In some embodiments, the stearate is selected from PEG-40 stearate, glyceryl steatrate, sorbitan tristearate, stearyl alcohol and mixtures thereof.

In some embodiments, the stearate is glyceryl stearate.

In still other embodiments, the inert additive is an emollient, being selected from vegetable and animal fats and oils such as castor oil, hydrogenated castor oil, cocoa butter, safflower oil, cottonseed oil, corn oil, olive oil, cod liver oil, almond oil, avocado oil, palm oil, sesame oil, squalene, phytosqalene, kikui oil, chamomilla recutita (matricaria) flower oil, hypericum perforatum oil, soybean oil and vitis vinifera (grape) seed oil; acetoglyceride esters, such as acetylated monoglycerides; alkyl esters of fatty acids having 10 to 24 carbon atoms which include, but are not limited to, methyl, isopropyl, and butyl esters of fatty acids such as hexyl laurate, isohexyl laurate, ethylhexyl palmitate, isohexyl palmitate, isopropyl palmitate, octyl palmitate, decyloleate, isodecyl oleate, hexadecyl stearate decyl stearate, isopropyl isostearate, diisopropyl adipate, diisohexyl adipate, dihexyldecyl adipate, diisopropyl sebacate, lauryl lactate, myristyl lactate, and cetyl lactate; alkenyl esters of fatty acids having 10 to 20 carbon atoms such as oleyl myristate, oleyl stearate, and oleyl oleate; fatty acids having 10 to 20 carbon atoms such as pelargonic, lauric, myristic, palmitic, stearic, isostearic, hydroxystearic, oleic, linoleic, ricinoleic, arachidic, behenic, and erucic acids; fatty alcohols having 10 to 20 carbon atoms such as lauryl, myristyl, cetyl, hexadecyl, stearyl, isostearyl, hydroxystearyl, oleyl, ricinoleyl, behenyl, erucyl, and 2-octyl dodecanyl alcohols; fatty alcohol ethers such as propoxylated fatty alcohols of 10 to 20 carbon atoms which include, but are not limited to, lauryl, cetyl, stearyl, isostearyl, oleyl, and cholesterol alcohols, having attached thereto from 1 to 50 propylene oxide groups; lanolin and lanolin derivatives such as lanolin, lanolin oil, lanolin wax, lanolin alcohols, lanolin fatty acids, isopropyl lanolate, ethoxylated lanolin, ethoxylated lanolin alcohols, ethoxylated cholesterol, propoxylated lanolin alcohols, acetylated lanolin alcohols, lanolin alcohols linoleate, lanolin alcohols ricinoleate, acetate of lanolin alcohols ricinoleate, acetate of ethoxylated alcohols-esters, bydrogenolysis of lanolin, ethoxylated sorbitol lanolin, and liquid and semisolid lanolin absorption bases; polyhydric alcohol esters such as ethylene glycol mono and di-fatty acid esters, diethylene glycol mono-and di-fatty acid esters, polyethylene glycol (200-6000) mono-and di-fatty acid esters, propylene glycol mono-and di-fatty acid esters,

polypropylene glycol 2000 monooleate, polypropylene glycol 2000 monostearate, glyceryl mono-and di-fatty acid esters, polyglycerol polyfatty esters, ethoxylated glyceryl monostearate, 1,2-butylene glycol monostearate, 1,2-butylene glycol distearate, polyoxyethylene polyol fatty acid ester, sorbitan fatty acid esters, and polyoxyethylene sorbitan fatty acid esters; Wax esters such as beeswax, spermaceti, myristyl myristate, stearyl stearate; forming a mixture of ether esters; vegetable waxes including, but not limited to, carnauba and candelilla waxes; surface active silicone derivatives such as cyclopentasiloxane PEG/PPG-18/18 dimethicone, dimethicone, dimethicone crosspolymer, cyclomethicone, cyclomethicone&dimethiconol; caprylic/capric triglyceride; and cholesterol fatty acid esters and any mixtures thereof.

In some embodiments, each of the at least one inert additive may constitute between about 0.05 to 15% of the total weight of the formulation. In some embodiments, the at least one inert additive constitutes between 0.05% and 10% or between 0.05% and 8%, or between 0.05% and 7%, or between 0.05% and 6%, or between 0.05% and 5% of the total weight of the formulation.

In other embodiments, the effect-inducing additive is selected from an anti-acne agent, an anti-aging agent, an antibacterial agent, an anti-cellulites agent, an antidandruff agent, an antifungal agent, an anti-inflammatory agent, an anti-irritation agent (e.g., allantoin, Aloe Barbadensis leaf juice), an antimicrobial agent, an antioxidant (e.g., butylated hydroxyanisole, propyl gallate), an antiperspirant agent, an antiseptic agent, a cell stimulant, a cleansing agent, a conditioner, a deodorant, a fragrance ingredient (e.g., perfume, limonene), a depilatory, a detergent, an enzyme, an essential oil, an exfoliant, a fungicide, a glosser, hair conditioner (hair conditioner agent), hair set resin, hair sheen agent, hair waving agent, a humectants (e.g., Erythritol, Homarine HCl, Ceratonia Siliqua (carob bean) gum), a moisturizer (e.g., sodium hyaluronate), an ointment base, a perfume, a protein, a skin calming agent, a skin cleanser, a skin conditioner (skin conditioning agent) , a skin healing agent, a skin lightening agent, a skin protectant, a skin smoothing agent, a skin softening agent, a skin soothing agent, a sunscreen agent, a tanning accelerator, vitamins, a colorant, and a flavoring agent.

In some embodiments, the at least one additive is a sunscreen, such as Ethyl hexyl methoxycinnamate or titanium dioxide.

In some embodiments, each of the at least one effect-inducing additive may constitute between about 0.05 to 15% of the total weight of the formulation. In some

embodiments, the at least one inert additive constitutes between 0.05% and 10% or between 0.05% and 8%, or between 0.05% and 7%, or between 0.05% and 6%, or between 0.05% and 5% of the total weight of the formulation.

The cosmetic or pharmaceutical compositions of the invention may also comprise pharmaceutical actives useful in the form of a chemical substance, material or compound, e.g., suitable for topical administration, to induce a desired local or systemic effect. Non-limiting examples of such actives are an antibiotic, an antiviral agent, an analgesic (e.g. ibuprofen, acetyl salicylic acid, naproxen, and the like), an antihistamine, an anti-inflammatory agent, an antipruritic, an antipyretic, an anesthetic agent, a diagnostic agent, a hormone, an antifungal agent, an antimicrobial agent, a cutaneous growth enhancer, a pigment modulator, an antiproliferative, an antipsoriatic, a retinoid, an anti-acne medicament (e.g. benzoyl peroxide, sulfur, and the like), an antineoplastic agent, a phototherapeutic agent, a keratolys (e.g. resorcinol, salicylic acid, and the like) and mixtures thereof.

Application of a composition of the invention onto the skin of a subject, for cosmetic/skin-care or therapeutic purposes may be in a single dose, in multiple doses, in a continuous or intermittent manner, depending, for example, upon the subject's physiological condition, whether the purpose of the administration is cosmetic or therapeutic/prophylactic and other factors known to the medical practitioner. The application of a composition of the invention may be essentially continuous over a pre-selected period of time or may be in a series of spaced doses.

The compositions of the invention are typically prepared by combining the ingredients of the active combination in appropriate concentrations. Other active or inert additives selected by one of skill in the art may optionally be added. The absolute weight of a given active agent included in a unit dose can vary widely. For example, about 0.1 microgram to about 5 g, or about 1 microgram to about 1 g, or about 10 microgram to about 500 mg, of at least one of the components can be administered by topical administration.

The compositions of the invention, being substantially for topical use, may be a skin-care formulation or a therapeutic formulation.

In some embodiments, the compositions of the invention are skin-care or dermo-pharmaceutical compositions (including, e.g., toiletries, health and beauty aids and cosmeceuticals) used for cosmetic and personal skin-care applications.

The term "***cosmetic composition***" or "***skin care composition***" relates to a composition of the invention that can be used for cosmetic purposes, purposes of hygiene or skin-care or as a basis for delivery of one or more pharmaceutical ingredients. It is also possible that these compositions are used for two or more of these same purposes at one time. For example, a medicated dandruff shampoo may be used as a personal care product, i.e., to provide clean hair, and at the same time have pharmacological properties.

In some embodiments, the cosmetic compositions are for promoting bodily attractiveness, cover or mask the physical manifestations of a disorder or disease, modulate or alleviate wrinkling, unevenness and dryness in the skin of a mammal. The compositions additionally regulate skin condition and signs of skin aging (all perceptible manifestations as well as any other macro or micro effects) by regulating visible and/or tactile discontinuities in skin texture, including fine lines, wrinkles, enlarged pores, roughness and other skin texture discontinuities associated with aged skin with reduced irritation and dryness.

In some embodiments, the cosmetic compositions are for one or more of skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity (anti dullness).

In another one of its aspects the present invention provides a composition (formulation) according to the invention for one or more of protecting and/or improving the state of the skin, and preventing and/or treating imperfections of the skin of a subject in need thereof.

In a further one of its aspects the present invention provides a composition (formulation) according to the invention for use in a method of one or more of protecting and/or improving the state of the skin, and preventing and/or treating imperfections of the skin of a subject in need thereof.

Yet in a further one of its aspects the present invention provides a method of one or more of protecting and/or improving the state of the skin, and preventing and/or treating imperfections of the skin of a subject in need thereof, the method comprising topically administering a composition according to the invention onto the skin of the subject.

In some embodiments the aforementioned protecting, improving, preventing and treating are associated with enhanced activity of LOX induced by the composition of the

invention and/or with reduction in collagen degradation caused by the composition of the invention.

In some embodiments, the methods/uses are for protecting and/or improving the state of the skin.

In some embodiments, the methods/uses are for preventing and/or treating imperfections of the skin of a subject.

In some embodiments, the composition of the invention is for use in a method for protecting and/or improving the state of the skin.

In some embodiments, the composition of the invention is for use in a method for preventing and/or treating imperfections of the skin of a subject.

In some embodiments the methods/uses disclosed herein are for one or more of skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity (anti dullness).

In a further one of its aspects the present invention provides a method for one or more of skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity (anti dullness), the method comprising topical administration of the composition according to the invention onto the skin of a subject in need thereof.

In yet a further one of its aspects the present invention provides use of the composition of the invention in a method for one or more of skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity (anti dullness), wherein the method comprises topical administration of the composition according to the invention onto the skin of a subject in need thereof.

Yet in a further one of its aspects the present invention provides the composition of the invention for use in a method for one or more of skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity (anti dullness), wherein the method comprises topical administration of the composition according to the invention onto the skin of a subject in need thereof.

In a further one of its aspects the present invention provides the use of a composition according to the invention for the preparation of a topical formulation (e.g., skin-care and/or pharmaceutical) wherein said topical formulation is for one or more of skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity (anti dullness).

In a further one of its aspects the present invention provides a composition for use in improving one or more of skin firmness and skin elasticity.

In a further one of its aspects the present invention provides a method of improving one or more of skin firmness and skin elasticity, wherein said method comprises topical application of the composition according to the invention onto the skin of a subject.

In a further one of its aspects the present invention provides the use of a composition according to the invention for the preparation of a topical formulation (e.g., skin-care and/or pharmaceutical) wherein said topical formulation is for improving one or more of skin firmness and skin elasticity.

In some embodiments the improving of one or more of skin firmness and skin elasticity is associated with enhanced activity of LOX induced by the composition of the invention and/or with reduction in collagen degradation caused by the composition.

In a further one of its aspects the present invention provides a composition for use in improving one or more of skin firmness and skin elasticity, wherein the improving is associated with enhanced activity of LOX induced by the composition and/or with reduction in collagen degradation caused by the composition.

In some embodiments, the composition of the invention is a pharmaceutical composition used in the treatment and/or prevention of at least one disease or disorder (e.g., of the skin).

In some embodiments the treatment and/or prevention is associated with enhanced activity of LOX induced by the composition and/or with reduction in collagen degradation caused by the composition.

In a further one of its aspects the present invention provides a method for treating and/or preventing a disease or disorder of the skin of a subject, wherein said method comprises topical application onto the skin of a subject in need thereof a composition according to the invention.

In yet a further one of its aspects the present invention provides a method for treating and/or preventing a disease or disorder of the skin of a subject, wherein said method comprises topical application onto the skin of a subject in need thereof a composition according to the invention, and wherein said treating and/or preventing is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

In another one of its aspects the present invention provides a use of at least one Dead Sea extract and at least one Haloarchaea extract for the preparation of a composition.

The compositions of the invention, in some embodiments, are formulated for use in the treatment of a disease or disorder.

Thus, the present invention also provides a method of therapeutic treatment or prophylaxis of such disease or disorder.

In some embodiments the disease or disorder is skin related.

In a further one of its aspects the present invention provides a method for treating a disease or disorder of the skin, the method comprising administering to a subject in need thereof a composition according to the invention.

In some embodiments the administration is topical administration.

In some embodiments, the subject is suffering, or has predisposition to suffer, or is one which may be exposed to conditions which increase the chances of suffering from a disease or disorder of the skin, which is optionally (may or may not be) related to one or more of age, sex, skin color, skin wounds, inflammation, irritation, a pre-existence of a disease not associated with the skin, etc.

In some embodiments, the disease or disorder of the skin is a secondary condition, e.g., inflammation, being related to an existing condition.

In further embodiments, the disease or disorder of the skin are age-related.

Non-limiting examples of such diseases or disorders of the skin are wounds, acne, psoriasis, atopic skin, diabetic skin, dermatitis, eczema, xerotic, dry skin, and chaffed skin.

In some embodiments, the administration is topical.

In some embodiments, the methods/uses disclosed herein are associate with non-medical condition/s of the skin.

In some embodiments, the method/s uses disclosed herein are associate with medical condition/s of the skin.

Yet, in a further one of its aspects the present invention provides a method for one or more of inhibiting collagen degradation and increasing the activity of LOX, wherein said method comprises topically administering the composition according to the invention onto the skin of a subject.

In another one of its aspects the present invention provides a composition for use in a method for one or more of inhibiting collagen degradation and increasing the activity of LOX, wherein said method comprises topically administering the composition according to the invention onto the skin of a subject.

In yet a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation for one or more of inhibiting collagen degradation and increasing the activity of LOX.

Yet, in a further one of its aspects the present invention provides a method for inhibiting collagen degradation, wherein said method comprises topically administering the composition according to the invention onto the skin of a subject.

In another one of its aspects the present invention provides a composition for use in a method of inhibiting collagen degradation, wherein said method comprises topically administering the composition according to the invention onto the skin of a subject.

In yet a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation for inhibiting collagen degradation.

In a further one of its aspects the present invention provides a method for increasing the activity of LOX, wherein said method comprises topically administering the composition according to the invention onto the skin of the subject, to thereby induce cross-linking of collagen and stabilize collagen fibrils.

In yet a further one of its aspects the present invention provides a composition for use in a method of increasing the activity of LOX, wherein said method comprises topically administering the composition according to the invention onto the skin of the subject, to thereby induce cross-linking of collagen and stabilize collagen fibrils.

In a further one of its aspects the present invention provides a method for stabilizing collagen fibrils, wherein said method comprises topically administering the composition according to the invention onto the skin of the subject, said administration increases the activity of LOX to induce cross-linking of collagen, thereby stabilizing collagen fibrils.

In yet a further one of its aspects the present invention provides a composition for use in a method for stabilizing collagen fibrils, wherein said method comprises topically

administering the composition according to the invention onto the skin of the subject, said administration increases the activity of LOX to induce cross-linking of collagen, thereby stabilizing collagen fibrils.

Yet, in another one of its aspects the present invention provides a method for treating and/or preventing inflammation of the skin of a subject, wherein said method comprises topically administering to a subject in need thereof a composition according to the invention.

In another one of its aspects the present invention provides a method for treating and/or preventing inflammation of the skin of a subject, wherein said method comprises topically administering to a subject in need thereof a composition according to the invention, and wherein said treating and/or preventing is associated with reduction in one or more of IL-1β and IL-6 skin levels caused by said composition.

In another one of its aspects the present invention provides a composition for use in method for treating and/or preventing inflammation of the skin of a subject, wherein said method comprises topically administering to a subject in need thereof a composition according to the invention.

In a further one of its aspects the present invention provides a composition for use in a method for treating and/or preventing inflammation of the skin of a subject, wherein said method comprises topically administering to a subject in need thereof a composition according to the invention, and wherein said treating and/or preventing is associated with reduction in one or more of IL-1β and IL-6 skin levels caused by said composition.

In a further one of its aspects the present invention provides the composition according to the invention for use in a method of enriching at least a region of a skin of a subject with hyaluronic acid, wherein said method comprises application of said composition onto at least a region of a skin of the subject.

In yet a further one of its aspects the present invention provides a method of enriching a skin of a subject with hyaluronic acid, wherein said method comprises applying onto at least a region of a skin of said subject a composition according to the invention.

Yet, in a further one of its aspects the present invention provides the use of a composition according to the invention for the preparation of a topical formulation (e.g., skin-care and/or pharmaceutical) wherein said topical formulation is for enriching a skin cell with hyaluronic acid.

In a further one of its aspects the present invention provides the use of a composition according to the invention for the preparation of a topical formulation (e.g., skin-care and/or pharmaceutical) wherein said topical formulation is for stabilizing collagen fibrils.

In another one of its aspects the present invention provides the use of a composition according to the invention for the preparation of a topical formulation (e.g., skin-care and/or pharmaceutical) wherein said topical formulation is for stabilizing collagen fibrils, wherein the formulation increases the activity of LOX upon topical application to induce cross-linking of collagen, thereby stabilizing collagen fibrils.

In another one of its aspects the present invention provides a method for one or more of treating and/or preventing skin disease or disorder; protecting and/or improving the state of the skin; and preventing and/or treating imperfections of the skin, wherein said method comprises administration (e.g., topical) the composition according to the invention to a subject in need thereof, and wherein the disease and/or disorder and/or the state of the skin and/or the imperfections of the skin are associated with and/or are mediated by and/or are affected by and/or are related to the collagen degradation (WIKI) biological pathway.

In a further one of its aspects the present invention provides a composition according to the present invention for use in a method for one or more of treating and/or preventing skin disease or disorder; protecting and/or improving the state of the skin; and preventing and/or treating imperfections of the skin, wherein said method comprises administration (e.g., topical) said composition to a subject in need thereof, and wherein the disease and/or disorder and/or the state of the skin and/or the imperfections of the skin are associated with and/or are mediated by and/or are affected by and/or are related to the collagen degradation (WIKI) biological pathway.

Yet in a further one of its aspects the present invention provides the use of a composition according to the invention for the preparation of a topical formulation (e.g., skin-care and/or pharmaceutical) wherein said topical formulation is for one or more of treating and/or preventing skin disease or disorder; protecting and/or improving the state of the skin; and preventing and/or treating imperfections of the skin, and wherein the disease and/or disorder and/or the state of the skin and/or the imperfections of the skin are associated with and/or are mediated by and/or are affected by and/or are related to the collagen degradation (WIKI) biological pathway.

One or more of the various methods and/or uses of the compositions as disclosed herein above and below (e.g., cosmetic and/or therapeutic) may be associate with one or more of (i) enhanced skin activity of LOX; (ii) reduction in skin collagen degradation; (iii) enrichment of the skin with hyaluronic acid; (iv) reduction in skin IL-1β levels; and (v) reduction in skin IL-6 levels, induced/caused by the composition of the present invention.

One or more of the methods and/or the uses of the compositions as disclosed herein above and below may also be further associated with and/or mediated by and/or affected by and/or related to the collagen degradation biological pathway.

Non limiting disorders/diseases/conditions that may be associated with and/or mediated by and/or affected by and/or related to the collagen degradation (WIKI) biological pathway are lupus, rheumatoid arthritis and aging, in particular skin related lupus, rheumatoid arthritis and aging.

Other attributes and indications (therapeutic and/or cosmetic) of the composition of the invention as described herein above and below may be associated with and/or mediated by and/or affected by and/or related to the collagen degradation (WIKI) biological pathway.

In a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation for one or more of treating and/or preventing a disease or disorder (e.g., of the skin); protecting and/or improving the state of the skin; and preventing and/or treating imperfections of the skin of a subject.

In a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation for one or more of treating and/or preventing a disease or disorder (e.g., of the skin); protecting and/or improving the state of the skin; preventing and/or treating imperfections of the skin of a subject; inhibiting collagen degradation; increasing the activity of LOX; treating and/or preventing inflammation of the skin of a subject; improving one or more of skin firmness and skin elasticity; and enriching at least a region of a skin of a subject with hyaluronic acid.

In further aspects the present invention provides a composition for use in, a composition for use in a method of, and use of the composition of the invention in the manufacture of a formulation (e.g., a pharmaceutical formulation and/or a skin care formulation) for, one or more of:

(i) protecting and/or improving the state of the skin, and preventing and/or treating imperfections of the skin of a subject;

(ii) treating and/or preventing at least one disease or disorder e.g., treating and/or preventing inflammation of the skin of a subject;

(iii) improving one or more of skin firmness and skin elasticity;

(iv) inhibiting collagen degradation;

(v) increasing the activity of LOX;

(vi) enriching at least a region of a skin of a subject with hyaluronic acid;

(vii) stabilizing collagen fibrils; and

(viii) skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity (anti dullness).

In some embodiments, the composition of the invention is a synergistic composition, illustrating a synergistic effect of the combination of the at least one Dead Sea extract and the at least one extract of Haloarchaea, the synergistic effect is illustrated in one or more of:

(i) protecting and/or improving the state of the skin, and preventing and/or treating imperfections of the skin of a subject;

(ii) treating and/or preventing at least one disease or disorder e.g., treating and/or preventing inflammation of the skin of a subject;

(iii) improving one or more of skin firmness and skin elasticity;

(iv) inhibiting collagen degradation;

(v) increasing the activity of LOX;

(vi) enriching at least a region of a skin of a subject with hyaluronic acid;

(vii) stabilizing collagen fibrils; and

(viii) skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity (anti dullness).

In some embodiments the synergistic effect is illustrated in reducing the expression of one or more genes that are related to the WIKI_COLLAGEN_DEGRADATION biological pathway. In some embodiments this

synergistic effect is reflected in a reduction which is greater than the additive reduction of the individual components i.e., the at least one Dead Sea extract and the at least one extract of Haloarchaea. At time, the reduction illustrated by the synergistic combination of the invention is 20% greater than the additive reduction illustrated by the individual components i.e., the at least one Dead Sea extract and the at least one extract of Haloarchaea. To this end, and in connection with the aspects described herein in connection with inhibiting collagen degradation, in some embodiments this inhibition is synergistic.

Accordingly, in a further one of its aspects the present invention provides a method for inhibiting collagen degradation, wherein said method comprises topically administering the composition according to the invention onto the skin of a subject, wherein the composition comprises a synergistically active combination of at least one Dead Sea extract and at least one extract of Haloarchaea which synergistically reduces the expression of various genes that are related to the WIKI_COLLAGEN_DEGRADATION biological pathway, to thereby (synergistically) inhibit collagen degradation.

In another one of its aspects the present invention provides a composition for use in a method inhibiting collagen degradation, wherein said method comprises topically administering the composition according to the invention onto the skin of a subject, wherein the composition comprises a synergistically active combination of at least one Dead Sea extract and at least one extract of Haloarchaea which synergistically reduces the expression of various genes that are related to the WIKI_COLLAGEN_DEGRADATION biological pathway, to thereby (synergistically) inhibit collagen degradation.

In yet a further one of its aspects the present invention provides the use of a composition according to the invention for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation for inhibiting collagen degradation, wherein the composition/formulation comprises a synergistically active combination of at least one Dead Sea extract and at least one extract of Haloarchaea which synergistically reduces the expression of various genes that are related to the WIKI_COLLAGEN_DEGRADATION biological pathway, to thereby (synergistically) inhibit collagen degradation.

In yet a further one of its aspects the present invention provides one or more of a lotion, an ointment, a gel, a mask, a toner, an essence, a shampoo, a moisturizer, a sunscreen, a cream, a stick, a spray, an aerosol, a foam, a paste, a mousse, a solid, semi-solid, or a liquid make-up, a foundation, and an eye make-up comprising the composition according to the invention.

In some embodiments the compositions of the present invention beneficially affect the skin via affecting one or more gene-expression and/or one or more protein expression.

In some embodiments the compositions of the present invention beneficially affect the skin at the molecular level e.g., by affecting (e.g., enhancing or reducing) the expression of one or more molecules that are involved in skin related conditions.

The term "***topical***" as used herein above and below refers to the application of a composition according to the invention directly onto at least a portion of a subject's skin (human's or non-human's skin) so as to achieve a desired effect, e.g., cosmetic or therapeutic effect, at the site of application. In some embodiments, the desired effect is achieved at the site of application without inducing one or more systemic effects. In other embodiments, the formulation of the invention induces at least a partial systemic effect which contributes to the induction of at least one desired effect.

The term "***skin***" as used herein above and below refers to any part of the human or animal skin, including the whole surface thereof, hair and nails.

The term "***treatment***" as used herein above and below refers to administration (e.g., topical) of an effective amount of a composition of the present invention effective to ameliorate undesired symptoms associated with a disease/disorder (e.g., skin disease), to prevent the manifestation of such symptoms before they occur, to slow down the progression of the disease, slow down the deterioration of symptoms, to enhance the onset of remission period, slow down the irreversible damage caused in the progressive chronic stage of the disease, to delay the onset of said progressive stage, to lessen the severity or cure the disease, to improve survival rate or more rapid recovery, or to prevent the disease form occurring or a combination of two or more of the above.

In some embodiments the disease and/or disorder is a non-medical condition e.g., associated with normal skin conditions.

In some embodiments the disease and/or disorder is a medical condition e.g., associate with pathological skin conditions.

The "***effective amount***", whether a therapeutically or cosmetically effective amount for purposes herein, is determined by such considerations as may be known in the art. The amount must be effective to achieve one or more of the above desired therapeutic or cosmetic effects, depending, *inter alia*, on the type and severity of the disease to be treated and the treatment regime. The effective amount is typically determined in appropriately designed clinical trials (dose range studies) and the person versed in the art will know how to properly conduct such trials in order to determine the effective amount. As generally known, an effective amount depends on a variety of factors including the affinity of the ligand to the receptor, its distribution profile, a variety of pharmacological parameters such as half-life on the skin, on undesired side effects, if any, on factors such as age and gender, etc.

As used herein above and below the term "***about***" refers to ± 10% of the indicated value.

Unless otherwise noted, the percentages of the various ingredients of the compositions of the present disclosure are provided herein in weight per weight ratio (w/w).

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

As used herein, the singular form "***a***", "***an***" and "***the***" include plural references unless the context clearly dictates otherwise. For example, the term "***an extract***" or "***at least one extract***" may independently include a plurality of extracts, including a variety thereof.

It is noted that various embodiments detailed herein above in connection with a specific aspect may be applicable to one or more other aspects of the invention.

Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find experimental support in the following examples.

DETAILED DESCRIPTION OF EMBODIMENTS

The following examples are not in any way intended to limit the scope of the invention as claimed.

Example 1: Dead Sea Extract

A commercial preparation of a Dead Sea extract referred to herein as "***Osmoter***" or "***Osmoter***^{TM}" or "**Mineral Skin Osmoter**" was used. The preparation is also known as "***Maris Sal***" or "***Maris Aqua***" (Dead Sea Water, DSW). The preparation is referred to herein below in the Examples and Figures also as "***OSM***".

Product name: Dead Sea Works LTD. The product comprises the following ions: Mg^{+2} (92,500 mg/L), Ca^{+2} (38,000 mg/L), K^{+} (1,400 mg/L), Na^{+} (2,000 mg/L), Sr^{+2} (800 mg/L), Cl^{-} (345,000 mg/L) and Br^{-} (11,500 mg/L).

Solutions comprising Dead Sea Water were prepared by dilutions of the "***Osmoter***" preparation in DDW (double distilled water). Various concentrations of the "***Osmoter***" preparation were used e.g., 0.1%, 0.25%, 0.3% and 0.5% (v/v). It is noted that the density of the studied solutions was very close to 1, thus, the v/v % presented herein is comparable to a w/w %.

Example 2: Regular Sea Water (SW)

Regular sea water (different from Dead Sea water) was used for comparison purposes (*See* below). To this end, sea water from the Mediterranean Sea was used. The regular sea water was sent to analysis. **Table 1** below details the sea water analysis.

Table 1: Sea water analysis

	Sea Water mg/L		Sea Water mg/L		Sea Water mg/L		Sea Water mg/L
Na	12,580	SO_4	3,100	Cu	< 0.01	Rb	0.11

K	442	As	< 0.05	Fe	0.23	Sb	< 0.05
Ca	495	B	36	Li	0.6	Sr	8.6
Mg	1,460	Ba	0.12	Mn	< 0.05	Th	< 0.05
Cl	22,700	Cd	< 0.01	Mo	< 0.02	U	< 0.05
Br	60	Co	< 0.05	Ni	< 0.05	V	< 0.05
SiO_2	330	Cr	< 0.1	Pb	0.17	Zn	0.5

Example 3: Halobacteria Extract

In the present disclosure the Halobacteria extract was purchased from Applied Biotechnologies, Germany.

Trade name: HALOCARE, antimicrobial stabilized with 1% PRESA-FERM.

Product reference: HC001.

Physical from: liquid.

The extract is soluble in water 100%, ethanol partly (10%).

Specifically, the HALOCARE biotechnological extract from Haloarchaea comprising a defined aqueous mixture of sulfated N-glycans (proteoglycans) (0.1-0.5ppm), lipids and squalene was used.

The extract is produced by a controlled fermentation of Haloarchaea followed by lysis of the cells. In particular, by the following process: culture by fermentation of Halobacterium salinarum (Haloarchaea) in a bioreactor. Extraction by osmo-lysis with water and sterilization by tyndallisation at 90°C (three times for 30 min). The extract is subsequently stabilized against microbial growth with PRESA-FERM. The starting substance is Inocula of Halobacterium salinarum (wildtype).

The International Nomenclature Cosmetic Ingredient (INCI) of the extract used: "*Halobacterium Ferment Lysate Extract*".

The Extract is one stabilized with 1% PRESA-FERM: LACTOCOCCUS FERMENT EXTRACT (INCI) 0.35%, and LACTOBACILLUS/ BRASSICA NIGRA SEED FERMENT EXTRACT (INCI) 0.65%.

Material regarding the extract used in the present disclosure is provided in **[10]**, the content of which is incorporated herein be reference.

Solutions comprising the Halobacteria Extract were prepared by dilutions of the extract in DDW (double distilled water). Various concentrations of the Halobacteria

Extract preparation were used e.g., 0.5%, 1.0% and 2.0% (w/w). The preparation is referred to herein below in the Examples and Figures also as "***HALO***". It is noted that the density of the studied solutions was very close to 1, thus, the v/v % presented herein is comparable to a w/w %.

Example 4: Human Dermal Fibroblast (HDF) lysyl oxidase (LOX) activity study

Human dermal fibroblasts (HDF) are cells within the dermis layer of skin responsible for generating connective tissue and allowing the skin to recover from injury. Furthermore, these dermal fibroblasts produce fibronectin and other extracellular matrix proteins such as collagen fibrin.

As noted above, Lysyl oxidase (LOX) is an extracellular enzyme that catalyzes the formation of aldehydes from lysine residues in collagen and elastin precursors. These aldehydes created by LOX are highly reactive, resulting in cross-linking collagen, which is essential for stabilizing collagen fibrils.

In the present study human dermal fibroblasts (HDF) Lysyl oxidase (LOX) activity of samples treated with Osmoter (OSM), Sea Water (SW) and Halobacteria extract (HALO) was tested without applying stress.

Protocol

Human primary fibroblast cell culture was grown at 80% confluence in Dulbecco's Modified Eagle's (DMEM) High glucose culture medium containing 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 U/ml streptomycin. The cells were cultivated in 6 wells plates.

The treatment solutions detailed in **Table 2** below were added to the culture medium (the final concentration is provided in v/v):

Table 2: Treatment solutions - Lysyl oxidase assay

#	**Treatment name**
1	Untreated
2	OSM 0.5% (v/v)
3	OSM 0.5% (v/v) + HALO 1.0% (v/v)
4	OSM 0.5% (v/v) + HALO 2.0% (v/v)
5	SW 0.5% (v/v)

6	SW 0.5% (v/v) + HALO 2.0% (v/v)
7	HALO 2.0% (v/v)

The cells were incubated at 37°C, 5% CO_2 at a 100% RH for 24 hours. After incubation, the medium was withdrawn and replaced by a new culture medium containing DMEM High glucose culture medium, 100 U/ml penicillin, and 100 U/ml streptomycin. The same treatment as listed in the above **Table 2** was added to this medium. The cells were incubated at 37°C, 5% CO_2 at a 100% RH for another 24 hours.

After incubation, the cells were extracted using a cell scraper and cold RIPA (Radioimmunoprecipitation assay) buffer. The RIPA with the cell's lysates were collected to a blending Eppendorf and ground using a bullet blender at max speed for 5 min.

The samples were centrifuged for 10 min at 10,000 rpm, and the supernatant was collected. BCA Protein concentration assay was performed on all the samples

The protein lysate samples were tested for LOX activity assay kit (Abcam, ab112139). In brief, a working solution mixture of HRP substrate solution (20µl), 50U/ml HRP solution (20µl), and assay buffer (5ml) was prepared. To 50µl of cell protein lysate transfer a 50µl of the working solution mixture. The solution was incubated at 37°C for 1 hr and read with a plate reader at Emission/ Excitation of 540/590 nm. Results were obtained as % of LOX activity per protein (µg/µl).

Figure 1 represents an experimental diagram of the above Human Dermal fibroblast (HDF) lysyl oxidase (LOX) activity assay.

Figure 2 illustrates the results obtained in the above LOX activity assay (as a % of untreated RF units) of HDF cells lysate. As noted, the cells were treated for 48 h with OSM, HALO, and SW. **Figure 2** represents 3 repetitions (n = 3). In **Figure 2** the symbol * (vs Untreated) represents P-value < 0.05; and the symbol # (OSM 0.5% vs Complex) represents P-value < 0.05.

Results: it is noted that the OSM 0.5% and the combinations of OSM and HALO (referred to herein at times as "***Complex***"), OSM 0.5%+HALO 1%, showed a significant elevation in the LOX activity. The elevation of LOX activity observed with the complex was significantly higher than that observed with the single ingredient OSM 0.5%. This effect is an opposite complementary effect to that observed with the study related to the

biological pathway WIKI_COLLAGEN_DEGRADATION (*See* **Example 7** and **Table 7** below).

Figure 3 illustrates the results obtained in the above LOX activity assay as a % of untreated and normalized to protein level (µg/µl).

Example 5: Human Dermal Fibroblast (HDF) and Hyaluronic Acid levels study

The effect of OSM, SW and HALO on Hyaluronic Acid levels was tested using the following protocol.

Protocol:

HDF was cultivated in 96 wells plate for 90% confluence. The cells were treated with the treatment solutions detailed in **Table 3** below for 24 hours with a medium that contained 89% DMEM culture medium, 10% Fetal Bovine Serum (FBS), 100 U/ml penicillin and 100 U/ml streptomycin. After 24 hr the medium was removed, and the wells were washed with PBS solution. Then, the wells were re-treatment with the same treatment with a culture medium that contained: 99% DMEM culture medium and 1% PSA. The HDF cells were irradiated with 20mJ/cm2 UVB radiation as a positive control. After 24 hr the medium was removed, and the wells were washed with PBS solution. The PBS solution was removed, and a cold (4°C) lysis buffer (50µl) was added to each well. The plate was transferred to 4°C overnight. The cell lysates were used for testing Hyaluronic Acid levels.

Table 3: Treatment solutions - Hyaluronic Acid assay

#	**Treatment name**
1	Untreated
2	Untreated + UVB 20mJ/cm2 control (at day 2, positive control)
3	OSM 0.5% (v/v)
4	HALO 1.0% (v/v)
5	OSM 0.5% (v/v) + HALO 1.0% (v/v)
6	SW 0.5% (v/v)

Figure 4 represents an experimental diagram of the above Human Dermal Fibroblast (HDF) and Hyaluronic Acid levels study.

Figure 5 illustrates the Hyaluronic Acid level present in HDF cells lysate after a total of 48 h incubation/treatment with OSM, SW and HALO extract, without stress. **Figure 5** represents 3 repetitions of the treated samples (n = 3) and 6 repetitions of the untreated sample (n=6). In **Figure 5** the symbol * (vs Untreated) represents P-value < 0.05; the symbol ** (vs Untreated) represents P-value < 0.0005; and the symbol # (OSM 0.5% vs Complex) represents P-value < 0.05.

Results: it is noted that the OSM 0.5% and the combinations of OSM and HALO (referred to herein at times as "***Complex***"), OSM 0.5%+HALO 1%, showed a significant elevation in the level of Hyaluronic acid in the HDF lysate. The elevation observed with the complex was significantly higher than that observed with the single ingredient OSM 0.5%.

Example 6: Human HaCaT cell line study in a premature aging model

HaCaT is an immortal keratinocyte cell line from adult human skin. HaCaT cells are utilized for their high capacity to differentiate and proliferate in vitro. In addition, their use in research allows for the characterization of human keratinocytes using a reproducible model. These cells are beneficial, such as short culture lifespan and variations between cell lines that would otherwise be encountered.

HaCaT cell lines were treated with OSM, SW and HALO extract after UVB radiation (mimicking premature aging) to assess the following cytokines level in cell lysate:

Interleukin 1 beta (IL-1β) is a cytokine protein. This cytokine is produced by activated macrophages as a proprotein. This cytokine is an important mediator of the inflammatory response and is involved in various cellular activities, including cell proliferation, differentiation and apoptosis.

Interleukin 6 (IL-6) is an interleukin that acts as a pro-inflammatory cytokine and an anti-inflammatory myokine. In addition, IL-6 is an essential mediator of fever and the acute phase response.

In the study the following protocol was used:

Protocol:

HaCaT cell line was cultivated in 96 wells plate for 100% confluence. The cells were treated with the treatment solutions detailed in **Table 4** below for 24 hours with a medium that contained 89% DMEM culture medium, 10% Fetal Bovine Serum FBS, and

1% Penicillin-Streptomycin-Amphotericin B Solution (PSA). After 24 hr the medium was removed, and the wells were washed with PBS solution. Then, the wells were irradiated with 20mJ/cm^2 UVB (except the untreated control) as stressor inducer. The PBS solution was redrawn, and the wells were post-treatment with the same treatment as the previous 24 h. After 24 h incubation, the wells were washed with PBS, and then the cells were prepared as lysate with the addition of 50µl cold (4°C) lysis buffer. The plate was kept at 4°C for 48 h. After incubation, the cell lysate was used to assess the cytokines level of IL-1β and IL-6.

In the study, cells viability was also tested utilizing the (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (MTT) assay following the protocol below:

MTT protocol

HaCaT cells were cultured in 96 wells plate at a 100% confluence. After treatment, the cell media was discarded, and the cells were washed one time with PBS solution. After the PBS solution was discarded, a 5mg/ml MTT solution diluted in PBS solution was added. The plate was incubated for 30 min at 37°C. After incubation, the MTT solution was discarded and Isopropyl alcohol was added to each well. The plate was allowed to stand at RT for 30 min under shaking. The plate was read at a plate reader at O.D of 570nm. Results were compared to the UVB radiated control. The results (not shown) indicated that the different treatment did not modulate the cells viability, indicating a non-toxic effect of the various treatments.

Figure 6 represents an experimental diagram of the above human HaCaT cell line study with UVB as a stressor inducer (mimicking premature aging).

Table 4: Treatment solutions - Human HaCaT cell line study

#	**Treatment name**
1	Untreated
2	Untreated + Stressor
3	OSM 0.5% (v/v)
4	HALO 1.0% (v/v)
5	OSM 0.5% (v/v) + HALO 1.0% (v/v)
6	SW 0.5% (v/v) + HALO 1.0% (v/v)

Figure 7 illustrates the Cytokine IL-1β level present in HaCaT cells lysate after treatment with OSM, SW and HALO extract and UVB 20mJ/cm^2 (irradiated for 24 hours with sample pre-incubation in the treatment solutions for 24 hours, i.e., 48 h total treatment). **Figure 7** represents 7 repetitions (n = 7) and Error bars = STD Error. In **Figure 7** the symbol ** (vs UVB 20mJ/cm^2) represents P-value < 0.0005.

Figure 8 illustrates the Cytokine IL-6 level present in HaCaT cells lysate after treatment with OSM, SW and HALO extract and UVB 20mJ/cm^2 (irradiated for 24 hours with sample pre-incubation in the treatment solutions for 24 hours, i.e., 48 h total treatment). **Figure 8** represents 7 repetitions (n = 7) and Error bars = STD Error. In **Figure 8** the symbol * (vs UVB 20mJ/cm^2) represents P-value < 0.05.

Results: it is noted that the HaCaT cell line that was pre- and post-treated with the ***"Complex"*** (OSM 0.5% +HALO 1%) and UVB radiation showed a significant reduction in IL-1β and IL-6 levels compared to the untreated control + UVB.

Example 7: Gene expression for biological pathways - microarray results in skin equivalents.

Biological activity on gene expression was performed using DNA microarray. The combination of OSM (0.5% v/v) + HALO (0.5% v/v) was tested and compared to the individual ingredients comprised therein and distilled water.

DNA microarray Procedure

Purpose

DNA microarrays can be used to screen for changes in the expression of hundreds to thousands of different genes, depending upon the gene chip set selected for the study.

Summary of Test Method

DNA microarrays are extremely powerful tools that allow users to analyze changes in gene expression by monitoring the RNA products of thousands of genes in a single experiment. Microarrays come in many forms, however the most popular form are comprised of glass microscope slides which have been studded with a large number of DNA fragments, also called *features*, with each feature containing a nucleotide

sequence that corresponds to a single specific gene. DNA microarrays are commonly used to compare treated and untreated cells/tissue to determine what changes in gene expression occur with the treatment.

Methods

Treatment

MatTek EFT-400 full thickness tissues were used as the model for this study. Upon arrival, the full thickness tissues were placed into 6 wells plates with 2 ml of culture media and incubated overnight at 37±2°C and 5±1% CO_2. After this overnight incubation the culture media was replaced with 5 ml of fresh media and the tissues were treated topically with the test materials prepared in distilled water as follows:

Table 5 details the various tested samples:

Table 5: tested samples in the microarray Procedure

#	**Treatment name**
1	Untreated control
2	Distilled Water (Water)
3	OSM 0.5% (v/v)
4	HALO 0.5% (v/v)
5	OSM 0.5% (v/v) + HALO 0.5% (v/v)

After the application of the test materials the tissues were incubated at 37±2°C and 5±1% CO_2 for 48 hours.

Total RNA Isolation (Ambion RNAqueous Kit)

At the end of the treatment period, the tissues were rinsed and transferred to a 2 ml centrifuge tube containing 700 µl of lysis buffer and homogenized. After centrifuging at 14,000 x g for 10 minutes at 4°C the supernatant from each tube was transferred to a new 1.5 ml tube and mixed with and equal volume of 64% ethanol. After mixing the solutions

was transferred to glass fiber filter cartridges and the cartridges were loaded into a 1.5 ml collection tube centrifuged for 1 minute at 14,000 RPM in a Napco 2002 Microcentrifuge with a DA-6T fixed angle rotor. The flow through was discarded and any remaining mixture was loaded into the filter cartridge and the centrifugation process was repeated until all of the mixture had been processed. The filter was then washed to remove any residual cellular debris from the RNA bound to the glass fibers by subsequently applying 700 µl of wash solution 1 (1 time) and 500 µl of wash solution 2 (2 times) to the filter cartridge and centrifuging at 14,000 RPM for 1 minute to pass each wash through the cartridge. After each wash, the flow through was discarded. After the final wash one final spin was performed without wash solution to remove any residual wash solution in the filter cartridge. The RNA bound to the glass fibers within the cartridge was then eluted by applying 40 µl of TE buffer (10 mM Tris-HCl, 1 mM EDTA, preheated to 70-80°C) to the cartridge and centrifuging the cartridge in a new collection tube at 14,000 RPM for one minute. The elution process was then repeated a second time using 20 µl of TE buffer.

mRNA Amplification (Ambion MessageAmp aRNA kit)

First Strand cDNA Synthesis: To start the first strand synthesis, 10 µl of total RNA for each sample was added to a 600 µl PCR tube and the total volume of liquid in the tube will be adjusted to 11 µl with DEPC H_2O. Next, 1 µl of T7 Oligo(dT) primer was added and the tube was incubated in a water bath at 70±2°C for 10 minutes to denature the RNA and then placed on ice to allow the primers to anneal to the poly A ends of the mRNA. After cooling 2 µl of 10x first strand buffer, 1 µl of RNAse inhibitor and 4 µl of dNTP mix were added to each tube, and the tube was incubated at 42°C in a hybridization oven (Labnet Problot). As soon as the tube was heated, 1 µl of Reverse Transcriptase was added and the tubes were returned to 42±2°C for 2 hours. At the end of the two hours the tubes were briefly centrifuged to collect all of the fluid at the bottom of the tube and then placed on ice.

Second Strand Synthesis and cDNA Purification: For the synthesis of the second strand of cDNA the following items were added to the tubes above (in this order): 63 µl DEPC H_2O, 10 µl 10x second strand buffer, 4 µl dNTP mix, 2 µl DNA Polymerase and 1 µl of RNAse H. The tubes were mixed and then incubated at 16±2°C for 2 hours in a

refrigerated centrifuge chamber (Precision Durafuge 300R with the rotor removed). Towards the end of the 2 hour incubation a sufficient quantity of DEPC H_2O was warmed to 50±2°C in a water bath and a cDNA purification filter cartridge was equilibrated with 50 µl of cDNA binding buffer (one cartridge per sample) for at least 5 minutes. After the samples finished incubating 250 µl of cDNA binding buffer was added to each tube and thoroughly mixed. The contents of the PCR tube were then transferred to the cDNA purification filter cartridge. The cartridge was then placed in a collection tube and centrifuged at 10,000 RPM for 1 minute. The flow-through was discarded and 650 µl of cDNA wash solution was added to the cartridge. The cartridge was centrifuged again and the flow- through was discarded, and then centrifuged one last time to ensure that the wash buffer had been completely emptied from the filter. The cDNA was eluted by applying 10 µl of preheated DEPC H_2O to the filter and centrifuging the filter in a new collection tube at 10,000 RPM for one minute. This elution was performed one additional time to give a total volume of 16-18 µl of recovered cDNA solution.

In Vitro Transcription to Synthesize aRNA and aRNA Purification: The in vitro transcription began by adding the following to the cDNA solution prepared above: 4 µl each of T7 ATP solution, T7 CTP solution, T7 GTP solution, T7 UTP solution, 4µl of 10x Reaction buffer, and 4 µl of T7 enzyme mix. The tube was mixed and then incubated at 37±2°C for 6-14 hours in a hybridization oven. Towards the end of the incubation a sufficient volume of Elution Solution was warmed to 50-60°C and an aRNA filter cartridge was equilibrated with 100 µl of aRNA binding buffer for at least 5 minutes. At the end of the incubation period, 350 µl of aRNA binding buffer was added to the sample tubes and thoroughly mixed. An additional 250 µl of absolute ethanol was also added to each tube. The mixture was then transferred to an aRNA filter cartridge; the cartridge was inserted into a collection tube and centrifuged at 10,000 RPM for 1 minute. The flow-through was discarded and 650 µl of aRNA wash buffer was added to the cartridge followed by centrifuging at 10,000 RPM for one minute. After discarding the flow through the cartridge was spun one final time to remove all traces of the wash buffer. The cartridge was then transferred to a new collection tube and 40 µl of pre-warmed Elution Solution was added to the cartridge. The cartridge was incubated for 2 minutes at room temperature and then the aRNA was eluted by centrifuging for 1 minute at 10,000 RPM. This elution was performed one additional time to give a total volume of 80 µl of aRNA

solution. The final concentration of the aRNA was determined by the Ribogreen assay described herein. In addition, the quality of the aRNA was checked via gel electrophoresis.

RNA Concentration Assay (Molecular Probes Ribogreen Assay)

The Ribogreen reagent is provided as a stock solution in DMSO. Prior to use the reagent was diluted 2000 fold in TE buffer. The RNA assay requires 200 µl of diluted Ribogreen reagent per sample to be tested and 1 ml of the reagent for the standards. A series of RNA standards was prepared by diluting purified ribosomal RNA derived from E. coli to the following concentrations: 1 µg/ml, 0.5 µg/ml, 0.1 µg/ml, 20 ng/ml and 0 ng/ml (blank). Prior to assaying, one microliter of the RNA samples prepared above was diluted 1000 fold in TE buffer. For the RNA assay, 100 µl of the diluted samples or standards was transferred to the wells of a black 96-well plate. The samples and standards were assayed in duplicate. After the samples/standards were added to the plate 100µl of the diluted Ribogreen assay reagent was added and the plate was gently mixed and allowed to incubate for 5-10 minutes protected from the light. After this incubation the plate was read with a Thermo Labsystems Fluorskan Ascent FL fluorometer using an excitation wavelength of 500 nm and an emission wavelength of 525 nm.

Labeling of aRNA with Fluorescent Dyes (PerkinElmer ASAP RNA Labeling Kit)

Two tubes were prepared for the labeling process, one for Cy3 labeling (green) and one for Cy5 labeling (red). To the Cy3 tube 2 µg of aRNA prepared from the untreated/control sample (the actual color assignment for each sample is not important, but for consistency Cy3 is normally used for the untreated sample) and enough DEPC H_2O was added to bring the total volume up to 4 µl. To the Cy5 tube 2 µg of aRNA prepared from the sample treated with the test material and enough DEPC H_2O was added to bring the total volume up to 4 µl. To both tubes 5 µl of ASAP labeling buffer was added along with 1 µl of the specific dye for the tube (Cy3 or Cy5). The tubes were incubated for 15 minutes at 85±2°C. At the end of the 15 minutes the tubes were placed on ice to cool them and then add 2.5 µl of ASAP stop solution was added to each tube.

Purification of Labeled aRNA

To purify the labeled aRNA, a Millipore Microcon YM-30 filter column was inserted into a collection tube and filled with 400 µl of TE buffer. The Cy3 and Cy5 probes were combined (6 µl of each or approximately 1 µg of each labeled aRNA) and then added to the microcon filter and thoroughly mixed with the TE buffer. The filter was centrifuged at 12,000 RPM for 8 minutes and the flow through was discarded. The column was then washed twice with 400 µl of TE buffer, discarding the flow though after each centrifugation (12,000 RPM for 8 minutes). After the final wash the filter column was inverted, placed into a new collection tube and centrifuged at 12,000 RPM for 2 minutes to collect the probe (the probe was concentrated in a volume of 2-30 µl of residual TE buffer).

Microarray Hybridization and W ashing (Agilent Technologies Microarrays)

For hybridization, 11 µl of 10x control target RNA (supplied with Agilent Technologies In Situ Hybridization Kit) was mixed with 30 µl of DEPC water and 2.5 µl of 25x Agilent Fragmentation Buffer. This mixture was allowed to incubate at 65°C for approximately 30 minutes in a hybridization oven. At the end of the incubation 55 µl of Agilent Hybridization Buffer was added along with the fluorescent aRNA probes prepared above. An Agilent SUREHYB hybridization chamber was prepared by inserting a glass gasket slide into the bottom half of the chamber and the hybridization mixture (approximately 110 µl) was applied to the glass gasket slide and a custom Agilent DNA Microarray Chip was placed face down on top of this gasket such that the hybridization solution was sandwiched between the glass gasket slide and the microarray face of the chip. The top half of the chamber was then attached and the connecting thumbscrew was tighten. After verifying that there was good bubble formation in the chamber, it was placed into the hybridization oven for approximately 17 hours (65°C and rotating at 4 RPM). At the end of the hybridization period the microarrays/glass gasket were removed from the SUREHYB chamber and placed in 50 ml of wash solution 1 (room temperature, 6x SSC, 0.005% Triton X-102). After the gasket had fallen away from the microarray, the array was placed in 300 ml of fresh wash solution 1 on a magnetic stir plate. The array was washed while the solution was mixed at medium speed for 10 minutes and then

transferred to 300 ml of wash solution 2 (0.1x SSX, 0.005% Triton X-102, 4°C) for 5 minutes. After the final wash the array was dried by centrifuging at 500 RPM for 5 minutes.

Microarray Scanning and Analysis

The microarrays were scanned with an Axon GenePix 4100A Scanner with the scanning resolution set to 5 µm and analyzed with GenePix Pro software. During the initial scan the PMT gains for the scanner were adjusted such that the cy5/cy3 image count ratios were between 0.95 and 1.05.

Calculations

Microarray Calculations

Fluorescence intensities for the microarrays were subjected to global normalization. The total fluorescent signal for both dyes were normalized to one to established a correction factor that would make the total intensities for both dyes equal. Criteria for evaluating changes in gene expression will vary from study to study however typically three criteria are required:

1. The ratio of Cy3/Cy5 (treated/untreated) fluorescence intensity is greater than 1.3 or less than 0.66. This relates to a change in gene expression of at least +/-30%.
2. The fluorescence intensity of the gene marker is greater than the background intensity.

Results

After scanning the arrays, the results were exported to an Excel spreadsheet. On each array, treated vs. control were compared. Each array was processed and the data was normalized from all arrays to get the average expression and log fold change (logFC- a known bioinformatics calculation method) for each gene on each array.

Figure 9 illustrates the Heatmap, Arrays Clustered by logFC observed for the tested samples. From the heatmap it can be seen that the patters of each of the tested samples are different, with different increased (red) or decreased (blue) genes (colors not shown in grayscale figure).

The number of up- or down-regulated genes for each array is listed in **Table 6** below.

Table 6: Down and Up regulated genes

Treatment name	Up-Regulated Genes	Down-Regulated Genes
Distilled Water (Water)	80	72
OSM 0.5% (v/v)	85	152
HALO 0.5% (v/v)	1568	342
OSM 0.5% (v/v) + HALO 0.5% (v/v)	1522	1734

To shed light on what biological pathways might be affected in the experiment, two methods were used to perform functional enrichment analysis. First, GSEA and all the genes ranked by adjusted logFC as input to GSEA. Second, a focus on the changes genes (up- regulated and down-regulated) was made and functional categories were looked for that show up more often in changed genes versus the whole genome (i.e., enriched).

A group of 32 pathways manually selected from KEGG and wiki-pathways were analyzed in detail as follows:

KEGG_TNF_SIGNALING_PATHWAY

KEGG_NF_KAPPA_B_SIGNLING_PATHWAY

WIKI_ACTIVATION_OF_MATRIX_METALLOPROTEINASES

WIKI_KERATINIZATION

WIKI_NRF2_PATHWAY

KEGG_APOPTOSIS

KEGG_TH1_AND_TH2_CELL_DIFFERENTIATION

KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY

KEEG_RETINOL_METABOLISM

KEGG_TIGHT_JUNCTION

KEGG_FATTY_ACID_BIOSYNTHESIS

KEGG_BASE_EXCISION_RAPAIR

KEGG_P53_SIGNALING_PATHWAY

KEGG_SIGNALING_PATHWAYS_REGULATING_PLURIPOTENCY_OF_STEM_CELLS

KEGG_CIRCADIAN_RHYTHM_MAMMAL

KEGG_NUCLEOTIDE_EXCISION_REPAIR

KEGG_SPHINGOLIPID_METABOLISM

KEGG_WNT_SIGNALING_PATHWAY

WIKI_COLLAGEN_DEGRADATION

WIKI_DEGRADATION_OF_THE_EXTRACELLULAR_MATRIX

WIKI_ASSEMBLY_OF_COLLAGEN_FIBRILS_AND_OTHER_MULTIMRIC_STRUCTURES

WIKI_EXTRACELLULAR_MATRIX_ORGANIZATION

WIKI_ELASTIC_FIBRE_FORMATION

KEGG_CELL_CYCLE

KEGG_GLYCOLYSIS_GLUCONEOGENESIS

WIKI_COLLAGEN_BIOSYNTHESIS_AND_MODIFYING_ENZYMES

WIKI_SPHINGOLIPID_METABOLISM

KEGG_FATTY_ACID_DEGRADATION

KEGG_PROTEASOME

KEGG_OXIDATIVE_PHOSPHORYLATION

WIKI_RESPIRATORY_ELECTRON_TRANSPORT_ATP_SYNTHESIS

WIKI_ELECTRON_TRANSPORT_CHAIN_IN_MITOCHONDRIA.

Bioconductor piano package was used to run PAGE enrichment of selected pathways using the logFC data from the arrays. From the PAGE analysis, each pathway is assigned a Z-sore and associated p-value and FDR values. A positive Z-score means that the pathway tends to be up-regulated, a negative Z-score means that the pathway tends to be down-regulated. Larger absolute value of Z-score, as well as small p-values mean more significant regulation.

Figure 10 illustrates a Heatmap showing all z-scores for 32 pathways selected from KEGG and wiki-pathways. From the Z-Score heatmap, it can be seen that the patters

of each of the tested samples are different, with different up regulated (red) or down regulated (blue) pathways (colors not shown in grayscale figure).

Table 7 represents a numeric data of the z-scores observed for the WIKI_COLLAGEN_DEGRADATION pathway.

Table 7: a numeric data of the z-scores observed for the WIKI_COLLAGEN_DEGRADATION pathway.

Biological pathway	**HALO** 0.5% (v/v)	**OSM** 0.5% (v/v) + **HALO** 0.5% (v/v)	**OSM** 0.5% (v/v)	**Water**
WIKI_COLLAGEN_DEGRADATION	-1.79	-2.23	-0.08	0.24

The WIKI_COLLAGEN_DEGRADATION biological pathway demonstrated an unexpected synergistic effect in the gene expression when comparing the combination (OSM+HALO) to the individual components HALO and OSM. Specifically, the combination reduced the gene expression of the genes that are related to said pathway to an extent of about 20% greater than that of the additive effect of the individual components.

The above observed effect is a complementary opposite effect to that observed in the results presented above in connection with LOX (*See* **Example 4** above). The combination of the OSM and the HALO not only synergistically reduced the gene expression of the genes that are related to collagen degradation, it also increased the LOX activity which is advantageous for example to collagen polymerization and to collagen fibrils stabilization.

The above results illustrate the beneficial effect of the complex of the invention on the skin that is associate with the related collagen function on the skin e.g., skin firmness and elasticity. This effect is advantageous in terms of inhibiting age-related skin damage and may be used as an anti-aging active combination e.g., in particular in older population of 60 years and above.

ILLUSTRATIVE EMBODIMENTS

The following embodiments are illustrative and not intended to limit the claimed subject matter. Further, the embodiments detailed herein above in connection with other aspects of the invention are considered relevant also to embodiments detailed herein below *mutatis mutandis*.

EMBODIMENT 1 A composition comprising at least one Dead Sea extract and at least one extract of Haloarchaea.

EMBODIMENT 2 The composition according to **EMBODIMENT 1**, wherein said Dead Sea extract is a mixture of natural materials obtained from the waters of the Dead Sea, the mud surrounding the Dead Sea and/or the soil bed of the Dead Sea.

EMBODIMENT 3 The composition according to **EMBODIMENT 1**, wherein said Dead Sea extract is the saline waters obtained from the Dead Sea.

EMBODIMENT 4 The composition according to **EMBODIMENT 3**, wherein the Dead Sea water has a specific density of 1.25-1.35 g/ml, pH of 4.6-5.6 (at 25°C), and less than 100 cfu/g of non-pathogenic microbes.

EMBODIMENT 5 The composition according to any one of **EMBODIMENTS 2** to **4**, wherein the Dead Sea water comprises Ca^{+2}, Cl^{-}, Mg^{+2}, Na^{+}, K^{+} and Br^{-}.

EMBODIMENT 6 The composition according to **EMBODIMENT 1**, wherein said Dead Sea extract is an aqueous solution simulating the salts and minerals content of the Dead Sea water.

EMBODIMENT 7 The composition according to any one of **EMBODIMENTS 1** to **6**, wherein said Dead Sea extract is the commercially available product Maris Sal.

EMBODIMENT 8 The composition according to any one of **EMBODIMENTS 1** to **7**, wherein said at least one extract of Haloarchaea is obtainable by a controlled fermentation of Haloarchaea, followed by lysis.

EMBODIMENT 9 The composition according to any one of **EMBODIMENTS 1** to **8**, wherein said at least one extract of Haloarchaea is an aqueous extract.

EMBODIMENT 10 The composition according to any one of **EMBODIMENTS 1** to **9**, wherein said at least one extract of Haloarchaea is an aqueous extract free of an organic solvent.

EMBODIMENT 11 The composition according to **EMBODIMENT 10**, wherein said organic solvent is one or more of a halogenated solvent (e.g., dichloromethane) and a C_1-C_4 alkanol (e.g., ethanol).

EMBODIMENT 12 The composition according to any one of **EMBODIMENTS 1** to **11**, wherein said at least one extract of Haloarchaea is an extract formulated with at least one additive.

EMBODIMENT 13 The composition according to **EMBODIMENT 12**, wherein said additive is a stabilizer, a diluent, a carrier, a filler, an antioxidant or any other inert additive.

EMBODIMENT 14 The composition according to any one of **EMBODIMENTS 1** to **13**, wherein said at least one extract of Haloarchaea is Halobacterium *salinarum* extract.

EMBODIMENT 15 The composition according to **EMBODIMENT 14**, wherein said Halobacterium *salinarum* is a wildtype Halobacterium *salinarum*.

EMBODIMENT 16 The composition according to **EMBODIMENT 14** or **15**, wherein said Halobacterium *salinarum* extract is a fraction enriched with one or more of sulfated N-glycans (proteoglycans), lipids and squalene.

EMBODIMENT 17 The composition according to any one of **EMBODIMENTS 14** to **16**, wherein said Halobacterium *salinarum* extract is obtainable by Halobacterium *salinarum* fermentation followed by lysis.

EMBODIMENT 18 The composition according to any one of **EMBODIMENTS 14** to **17**, wherein said Halobacterium *salinarum* extract is Halobacterium Ferment Lysate Extract (INCI).

EMBODIMENT 19 The composition according to any one **EMBODIMENTS 1** to **18**, wherein said Dead Sea extract is present in said composition at a concentration of between about 0.10% (w/w) to about 2.4 % (w/w).

EMBODIMENT 20 The composition according to **EMBODIMENT 19**, wherein said Dead Sea extract is present in said composition at a concentration of between about 0.5% (w/w) to about 2.4 % (w/w).

EMBODIMENT 21 The composition according to any one of **EMBODIMENTS 1** to **20**, wherein said at least one extract of Haloarchaea is present in said composition at a concentration of between about 0.1% (w/w) to about 2.0 % (w/w).

EMBODIMENT 22 The composition according to **EMBODIMENT 21**, wherein said at least one extract of Haloarchaea is present in said composition at a concentration of between about 0.5% (w/w) to about 2.0 % (w/w).

EMBODIMENT 23 The composition according to any one of the preceding **EMBODIMENTS**, being a composition selected from a skin-care and pharmaceutical composition.

EMBODIMENT 24 The composition according to **EMBODIMENT 23**, wherein said composition is for topical application.

EMBODIMENT 25 The composition according to any one of the preceding **EMBODIMENTS**, being a synergistic composition.

EMBODIMENT 26 The composition according to any one of the preceding **EMBODIMENTS**, being in the form selected from a lotion, an ointment, a gel, a mask, a toner, an essence, a cream, a water in oil or oil in water emulsion, a shampoo, a moisturizer, a sunscreen, a cream, a stick, a spray, an aerosol, a foam, a paste, a mousse, a solid, semi-solid, or a liquid make-up, a foundation, and an eye make-up.

EMBODIMENT 27 The composition according to any one of the preceding **EMBODIMENTS**, further comprising at least one additive selected from a diluent, a preservative, an abrasive, an anticaking agent, an antistatic agent, a binder, a buffer, a dispersant, an emollient, an emulsifier, a co-emulsifiers, a fiberous material, a film forming agent, a fixative, a foaming agent, a foam stabilizer, a foam booster, a gellant, a lubricant, a moisture barrier agent, a plasticizer, a preservative, a propellant, a stabilizer a surfactant, a suspending agent, a thickener, a wetting agent, and a liquefier.

EMBODIMENT 28 The composition according to any one of the preceding **EMBODIMENTS**, further comprising at least one additive selected from an anti-acne agent, an anti-aging agent, an antibacterial agent, an anti-cellulites agent, an antidandruff agent, an antifungal agent, an anti-inflammatory agent, an anti-irritation agent, an antimicrobial agent, an antioxidant agent, an antiperspirant agent, an antiseptic agent, a cell stimulant, a cleansing agent, a conditioner, a deodorant, a depilatory, a detergent, an enzyme, an essential oil, an exfoliant, a fungicide, a glosser, hair conditioner, hair set resin, hair sheen agent, hair waving agent, a humectants, a moisturizer, an ointment base, a perfume, a protein, a skin calming agent, a skin cleanser, a skin conditioner, a skin healing agent, a skin lightening agent, a skin protectant, a skin smoothing agent, a skin softening agent, a skin soothing agent, a sunscreen agent, a tanning accelerator, vitamins, a colorant, and a flavoring agent.

EMBODIMENT 29 The composition according to any one of the preceding **EMBODIMENTS**, for use in the preparation of a cosmetic/skin-care or a pharmaceutical composition.

EMBODIMENT 30 The composition according to any one of **EMBODIMENTS 1** to **28**, for use in one or more of protecting and/or improving the state of the skin, and preventing and/or treating imperfections of the skin of a subject.

EMBODIMENT 31 The composition according to **EMBODIMENT 30**, wherein said protecting and/or improving and/or preventing and/or treating are associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

EMBODIMENT 32 The composition according to any one of **EMBODIMENTS 1** to **28**, for use in improving one or more of skin firmness and skin elasticity.

EMBODIMENT 33 The composition according to **EMBODIMENT 32**, wherein said improving is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

EMBODIMENT 34 The composition according to any one of **EMBODIMENTS 1** to **28**, for use in treating and/or preventing at least one disease or disorder of the skin.

EMBODIMENT 35 The composition according to **EMBODIMENT 34**, wherein said treating and/or preventing is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

EMBODIMENT 36 The composition according to any one of **EMBODIMENTS 1** to **28**, for use in a method for one or more of inhibiting collagen degradation and increasing the activity of LOX, wherein said method comprises topically administering said composition onto the skin of a subject.

EMBODIMENT 37 The composition according to any one of **EMBODIMENTS 1** to **28**, for use in a method of inhibiting collagen degradation, wherein said method comprises topically administering said composition onto the skin of a subject.

EMBODIMENT 38 The composition according to any one of **EMBODIMENTS 1** to **28**, for use in a method of increasing the activity of LOX, wherein said method comprises topically administering said composition onto the skin of the subject, to thereby induce cross-linking of collagen and stabilize collagen fibrils.

EMBODIMENT 39 The composition according to any one of **EMBODIMENTS 1** to **28**, for use in a method for stabilizing collagen fibrils, wherein said method comprises

topically administering said composition onto the skin of the subject, said administration increases the activity of LOX to induce cross-linking of collagen, thereby stabilizing collagen fibrils.

EMBODIMENT 40 The composition according to any one of **EMBODIMENTS 1** to **28**, for use in a method for treating and/or preventing inflammation of the skin of a subject, wherein said method comprises administering to a subject in need thereof said composition.

EMBODIMENT 41 The composition according to **EMBODIMENT 40**, and wherein said treating and/or preventing is associated with reduction in one or more of IL-1β and IL-6 skin levels caused by said composition.

EMBODIMENT 42 The composition according to any one of **EMBODIMENTS 1** to **28**, for use in a method of enriching at least a region of a skin of a subject with hyaluronic acid, wherein said method comprises application of said composition onto at least a region of a skin of the subject.

EMBODIMENT 43 A method for one or more of protecting and/or improving the state of the skin of a subject and preventing and/or treating imperfections of the skin of a subject in need thereof, comprising topically administering the composition according to any one of **EMBODIMENTS 1** to **28** onto the skin of the subject.

EMBODIMENT 44 The method according to **EMBODIMENT 43**, wherein said protecting and/or improving and/or preventing and/or treating are associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

EMBODIMENT 45 A method of improving one or more of skin firmness and skin elasticity, comprising topical application of the composition according to any one of **EMBODIMENTS 1** to **28** onto the skin of a subject.

EMBODIMENT 46 The method according to **EMBODIMENT 45**, wherein said improving is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

EMBODIMENT 47 A method for treating and/or preventing a disease or disorder of the skin of a subject, comprising topical application onto the skin of a subject in need thereof the composition according to any one **EMBODIMENTS 1** to **28**.

EMBODIMENT 48 The method according to **EMBODIMENT 47**, wherein said treating and/or preventing is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

EMBODIMENT 49 A method for one or more of inhibiting collagen degradation and increasing the activity of LOX, comprising topical administration to a subject in need thereof the composition according to any one of **EMBODIMENTS 1** to **28**.

EMBODIMENT 50 A method of inhibiting collagen degradation, comprising topical administration to a subject in need thereof the composition according to any one of **EMBODIMENTS 1** to **28**.

EMBODIMENT 51 A method for increasing the activity of LOX, comprising topically administering the composition according to any one of **EMBODIMENTS 1** to **28** onto the skin of the subject, to thereby induce cross-linking of collagen and stabilize collagen fibrils.

EMBODIMENT 52 A method for stabilizing collagen fibrils, comprising topically administering the composition according to any one of **EMBODIMENTS 1** to **28** onto the skin of the subject, said administration increases the activity of LOX to induce cross-linking of collagen, thereby stabilizing collagen fibrils.

EMBODIMENT 53 A method for treating and/or preventing inflammation of the skin of a subject, comprising topically administering to a subject in need thereof the composition according to any one of **EMBODIMENTS 1** to **28**.

EMBODIMENT 54 The method according to **EMBODIMENT 53**, wherein said treating and/or preventing is associated with reduction in one or more of IL-1β and IL-6 skin levels caused by said composition.

EMBODIMENT 55 A method of enriching a skin of a subject with hyaluronic acid, comprising applying onto at least a region of a skin of said subject the composition according to any one of **EMBODIMENTS 1** to **28**.

EMBODIMENT 56 The composition for use according to any one of **EMBODIMENTS 30** to **42**, or the method according to any one **EMBODIMENTS 43** to **55**, wherein said use or method are associated with and/or are mediated by and/or are affected by and/or are related to collagen degradation (WIKI) biological pathway.

EMBODIMENT 57 The composition according to any one of **EMBODIMENTS 1** to **28**, for use in one or more of skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity.

EMBODIMENT 58 A method for one or more of skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity, comprising topical administration of the composition according to any one of **EMBODIMENTS 1** to **28** onto the skin of a subject in need thereof.

EMBODIMENT 59 A lotion, an ointment, a gel, a mask, a toner, an essence, a shampoo, a moisturizer, a sunscreen, a cream, a stick, a spray, an aerosol, a foam, a paste, a mousse, a solid, semi-solid, or a liquid make-up, a foundation, or an eye make-up comprising a composition according to any one of **EMBODIMENTS 1** to **28**.

EMBODIMENT 60 Use of a composition according to any one of **EMBODIMENTS 1** to **28** for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation.

EMBODIMENT 61 The use according to **EMBODIMENT 60**, wherein said composition/formulation is for one or more of:

(i) protecting and/or improving the state of the skin, and preventing and/or treating imperfections of the skin of a subject;

(ii) treating and/or preventing at least one disease or disorder e.g., treating and/or preventing inflammation of the skin of a subject;

(iii) improving one or more of skin firmness and skin elasticity;

(iv) inhibiting collagen degradation;

(v) increasing the activity of LOX;

(vi) enriching at least a region of a skin of a subject with hyaluronic acid;

(vii) stabilizing collagen fibrils; and

(viii) skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity.

CLAIMS:

1. A composition comprising at least one Dead Sea extract and at least one extract of Haloarchaea.

2. The composition according to Claim 1, wherein said Dead Sea extract is a mixture of natural materials obtained from the waters of the Dead Sea, the mud surrounding the Dead Sea and/or the soil bed of the Dead Sea.

3. The composition according to Claim 1, wherein said Dead Sea extract is the saline waters obtained from the Dead Sea.

4. The composition according to Claim 3, wherein the Dead Sea water has a specific density of 1.25-1.35 g/ml, pH of 4.6-5.6 (at 25°C), and less than 100 cfu/g of non-pathogenic microbes.

5. The composition according to any one of Claims 2 to 4, wherein the Dead Sea water comprises Ca^{+2}, Cl^{-}, Mg^{+2}, Na^{+}, K^{+} and Br^{-}.

6. The composition according to Claim 1, wherein said Dead Sea extract is an aqueous solution simulating the salts and minerals content of the Dead Sea water.

7. The composition according to any one of Claims 1 to 6, wherein said Dead Sea extract is the commercially available product Maris Sal.

8. The composition according to any one of Claims 1 to 7, wherein said at least one extract of Haloarchaea is obtainable by a controlled fermentation of Haloarchaea, followed by lysis.

9. The composition according to any one of Claims 1 to 8, wherein said at least one extract of Haloarchaea is an aqueous extract.

10. The composition according to any one of Claims 1 to 9, wherein said at least one extract of Haloarchaea is an aqueous extract free of an organic solvent.

11. The composition according to Claim 10, wherein said organic solvent is one or more of a halogenated solvent (e.g., dichloromethane) and a C_1-C_4 alkanol (e.g., ethanol).

12. The composition according to any one of Claims 1 to 11, wherein said at least one extract of Haloarchaea is an extract formulated with at least one additive.

13. The composition according to Claim 12, wherein said additive is a stabilizer, a diluent, a carrier, a filler, an antioxidant or any other inert additive.

14. The composition according to any one of Claims 1 to 13, wherein said at least one extract of Haloarchaea is Halobacterium *salinarum* extract.

15. The composition according to Claim 14, wherein said Halobacterium *salinarum* is a wildtype Halobacterium *salinarum*.

16. The composition according to Claim 14 or 15, wherein said Halobacterium *salinarum* extract is a fraction enriched with one or more of sulfated N-glycans (proteoglycans), lipids and squalene.

17. The composition according to any one of Claims 14 to 16, wherein said Halobacterium *salinarum* extract is obtainable by Halobacterium *salinarum* fermentation followed by lysis.

18. The composition according to any one of Claims 14 to 17, wherein said Halobacterium *salinarum* extract is Halobacterium Ferment Lysate Extract (INCI).

19. The composition according to any one of Claims 1 to 18, wherein said Dead Sea extract is present in said composition at a concentration of between about 0.10% (w/w) to about 2.4 % (w/w).

20. The composition according to Claim 19, wherein said Dead Sea extract is present in said composition at a concentration of between about 0.5% (w/w) to about 2.4 % (w/w).

21. The composition according to any one of Claims 1 to 20, wherein said at least one extract of Haloarchaea is present in said composition at a concentration of between about 0.1% (w/w) to about 2.0 % (w/w).

22. The composition according to Claim 21, wherein said at least one extract of Haloarchaea is present in said composition at a concentration of between about 0.5% (w/w) to about 2.0 % (w/w).

23. The composition according to any one of the preceding claims, being a composition selected from a skin-care and pharmaceutical composition.

24. The composition according to Claim 23, wherein said composition is for topical application.

25. The composition according to any one of the preceding claims, being a synergistic composition.

26. The composition according to any one of the preceding claims, being in the form selected from a lotion, an ointment, a gel, a mask, a toner, an essence, a cream, a water in oil or oil in water emulsion, a shampoo, a moisturizer, a sunscreen, a cream, a stick, a spray, an aerosol, a foam, a paste, a mousse, a solid, semi-solid, or a liquid make-up, a foundation, and an eye make-up.

27. The composition according to any one of the preceding claims, further comprising at least one additive selected from a diluent, a preservative, an abrasive, an anticaking agent, an antistatic agent, a binder, a buffer, a dispersant, an emollient, an emulsifier, a co-emulsifiers, a fiberous material, a film forming agent, a fixative, a foaming agent, a foam stabilizer, a foam booster, a gellant, a lubricant, a moisture barrier agent, a plasticizer, a preservative, a propellant, a stabilizer a surfactant, a suspending agent, a thickener, a wetting agent, and a liquefier.

28. The composition according to any one of the preceding claims, further comprising at least one additive selected from an anti-acne agent, an anti-aging agent, an antibacterial agent, an anti-cellulites agent, an antidandruff agent, an antifungal agent, an anti-inflammatory agent, an anti-irritation agent, an antimicrobial agent, an antioxidant agent, an antiperspirant agent, an antiseptic agent, a cell stimulant, a cleansing agent, a conditioner, a deodorant, a depilatory, a detergent, an enzyme, an essential oil, an exfoliant, a fungicide, a glosser, hair conditioner, hair set resin, hair sheen agent, hair waving agent, a humectants, a moisturizer, an ointment base, a perfume, a protein, a skin calming agent, a skin cleanser, a skin conditioner, a skin healing agent, a skin lightening agent, a skin protectant, a skin smoothing agent, a skin softening agent, a skin soothing agent, a sunscreen agent, a tanning accelerator, vitamins, a colorant, and a flavoring agent.

29. The composition according to any one of the preceding claims, for use in the preparation of a cosmetic/skin-care or a pharmaceutical composition.

30. The composition according to any one of Claims 1 to 28, for use in one or more of protecting and/or improving the state of the skin, and preventing and/or treating imperfections of the skin of a subject.

31. The composition according to Claim 30, wherein said protecting and/or improving and/or preventing and/or treating are associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

32. The composition according to any one of Claims 1 to 28, for use in improving one or more of skin firmness and skin elasticity.

33. The composition according to Claim 32, wherein said improving is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

34. The composition according to any one of Claims 1 to 28, for use in treating and/or preventing at least one disease or disorder of the skin.

35. The composition according to Claim 34, wherein said treating and/or preventing is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

36. The composition according to any one of Claims 1 to 28, for use in a method for one or more of inhibiting collagen degradation and increasing the activity of LOX, wherein said method comprises topically administering said composition onto the skin of a subject.

37. The composition according to any one of Claims 1 to 28, for use in a method of inhibiting collagen degradation, wherein said method comprises topically administering said composition onto the skin of a subject.

38. The composition according to any one of Claims 1 to 28, for use in a method of increasing the activity of LOX, wherein said method comprises topically administering said composition onto the skin of the subject, to thereby induce cross-linking of collagen and stabilize collagen fibrils.

39. The composition according to any one of Claims 1 to 28, for use in a method for stabilizing collagen fibrils, wherein said method comprises topically administering said composition onto the skin of the subject, said administration increases the activity of LOX to induce cross-linking of collagen, thereby stabilizing collagen fibrils.

40. The composition according to any one of Claims 1 to 28, for use in a method for treating and/or preventing inflammation of the skin of a subject, wherein said method comprises administering to a subject in need thereof said composition.

41. The composition according to Claim 40, and wherein said treating and/or preventing is associated with reduction in one or more of IL-1β and IL-6 skin levels caused by said composition.

42. The composition according to any one of Claims 1 to 28, for use in a method of enriching at least a region of a skin of a subject with hyaluronic acid, wherein said method comprises application of said composition onto at least a region of a skin of the subject.

43. A method for one or more of protecting and/or improving the state of the skin of a subject and preventing and/or treating imperfections of the skin of a subject in need thereof, comprising topically administering the composition according to any one of Claims 1 to 28 onto the skin of the subject.

44. The method according to Claim 43, wherein said protecting and/or improving and/or preventing and/or treating are associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

45. A method of improving one or more of skin firmness and skin elasticity, comprising topical application of the composition according to any one of Claims 1 to 28 onto the skin of a subject.

46. The method according to Claim 45, wherein said improving is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

47. A method for treating and/or preventing a disease or disorder of the skin of a subject, comprising topical application onto the skin of a subject in need thereof the composition according to any one of Claims 1 to 28.

48. The method according to Claim 47, wherein said treating and/or preventing is associated with enhanced activity of LOX induced by said composition and/or with reduction in collagen degradation caused by said composition.

49. A method for one or more of inhibiting collagen degradation and increasing the activity of LOX, comprising topical administration to a subject in need thereof the composition according to any one of Claims 1 to 28.

50. A method of inhibiting collagen degradation, comprising topical administration to a subject in need thereof the composition according to any one of Claims 1 to 28.

51. A method for increasing the activity of LOX, comprising topically administering the composition according to any one of Claims 1 to 28 onto the skin of the subject, to thereby induce cross-linking of collagen and stabilize collagen fibrils.

52. A method for stabilizing collagen fibrils, comprising topically administering the composition according to any one of Claims 1 to 28 onto the skin of the subject, said administration increases the activity of LOX to induce cross-linking of collagen, thereby stabilizing collagen fibrils.

53. A method for treating and/or preventing inflammation of the skin of a subject, comprising topically administering to a subject in need thereof the composition according to any one of Claims 1 to 28.

54. The method according to Claim 53, wherein said treating and/or preventing is associated with reduction in one or more of IL-1β and IL-6 skin levels caused by said composition.

55. A method of enriching a skin of a subject with hyaluronic acid, comprising applying onto at least a region of a skin of said subject the composition according to any one of Claims 1 to 28.

56. The composition for use according to any one of Claims 30 to 42, or the method according to any one of Claims 43 to 55, wherein said use or method are associated with and/or are mediated by and/or are affected by and/or are related to collagen degradation (WIKI) biological pathway.

57. The composition according to any one of Claims 1 to 28, for use in one or more of skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity.

58. A method for one or more of skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity, comprising topical administration of the composition according to any one of Claims 1 to 28 onto the skin of a subject in need thereof.

59. A lotion, an ointment, a gel, a mask, a toner, an essence, a shampoo, a moisturizer, a sunscreen, a cream, a stick, a spray, an aerosol, a foam, a paste, a mousse, a solid, semi-solid, or a liquid make-up, a foundation, or an eye make-up comprising a composition according to any one of Claims 1 to 28.

60. Use of a composition according to any one of Claims 1 to 28 for the manufacture of a pharmaceutical composition/formulation and/or a skin care composition/formulation.

61. The use according to Claim 60, wherein said composition/formulation is for one or more of:

(i) protecting and/or improving the state of the skin, and preventing and/or treating imperfections of the skin of a subject;

(ii) treating and/or preventing at least one disease or disorder e.g., treating and/or preventing inflammation of the skin of a subject;

(iii) improving one or more of skin firmness and skin elasticity;

(iv) inhibiting collagen degradation;

(v) increasing the activity of LOX;

(vi) enriching at least a region of a skin of a subject with hyaluronic acid;

(vii) stabilizing collagen fibrils; and

(viii) skin lifting and firming, restoring skincare for women 60 years and above, and restoring luminosity.

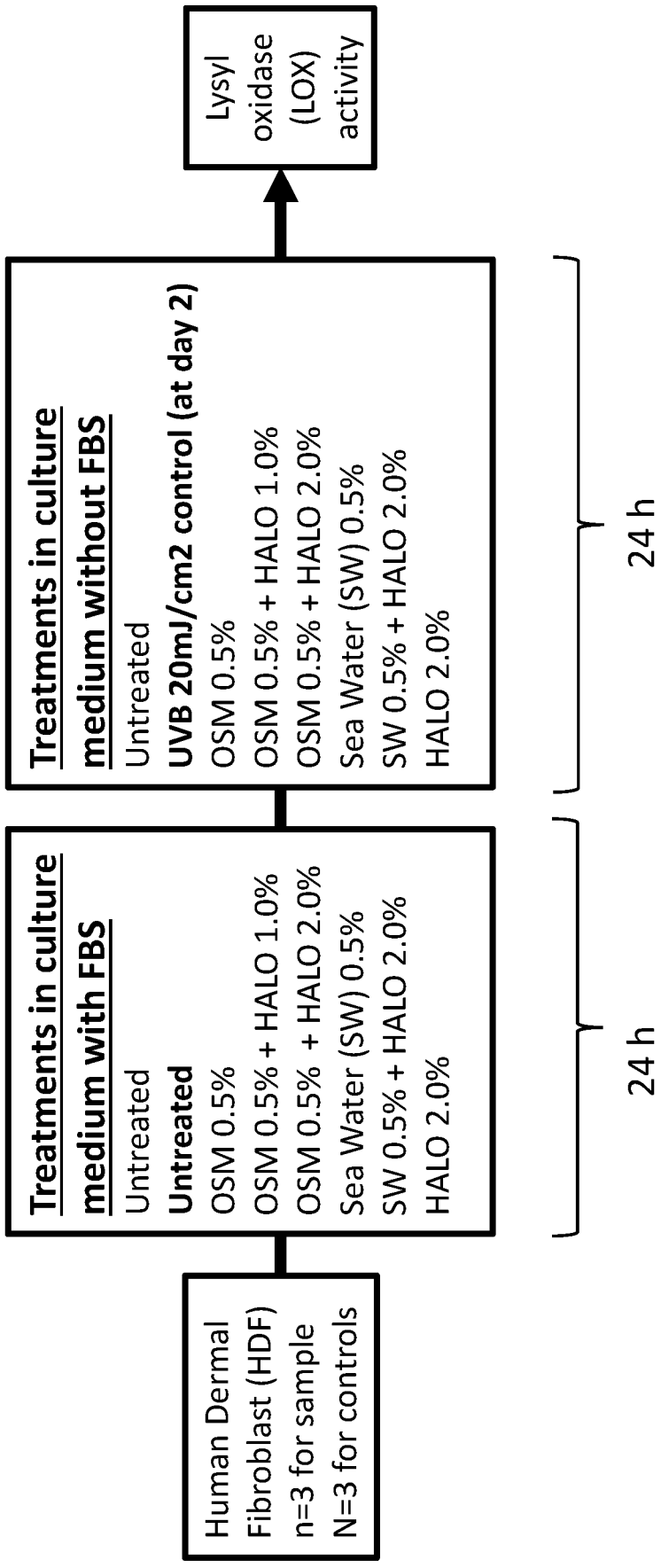

Human Dermal Fibroblast (HDF) n=3 for sample N=3 for controls
Treatments in culture medium with FBS
Untreated
Untreated
OSM 0.5%
OSM 0.5% + HALO 1.0%
OSM 0.5% + HALO 2.0%
Sea Water (SW) 0.5%
SW 0.5% + HALO 2.0%
HALO 2.0%
24 h
Treatments in culture medium without FBS
Untreated
UVB 20mJ/cm2 control (at day 2)
OSM 0.5%
OSM 0.5% + HALO 1.0%
OSM 0.5% + HALO 2.0%
Sea Water (SW) 0.5%
SW 0.5% + HALO 2.0%
HALO 2.0%
24 h
Lysyl oxidase (LOX) activity

Figure 1

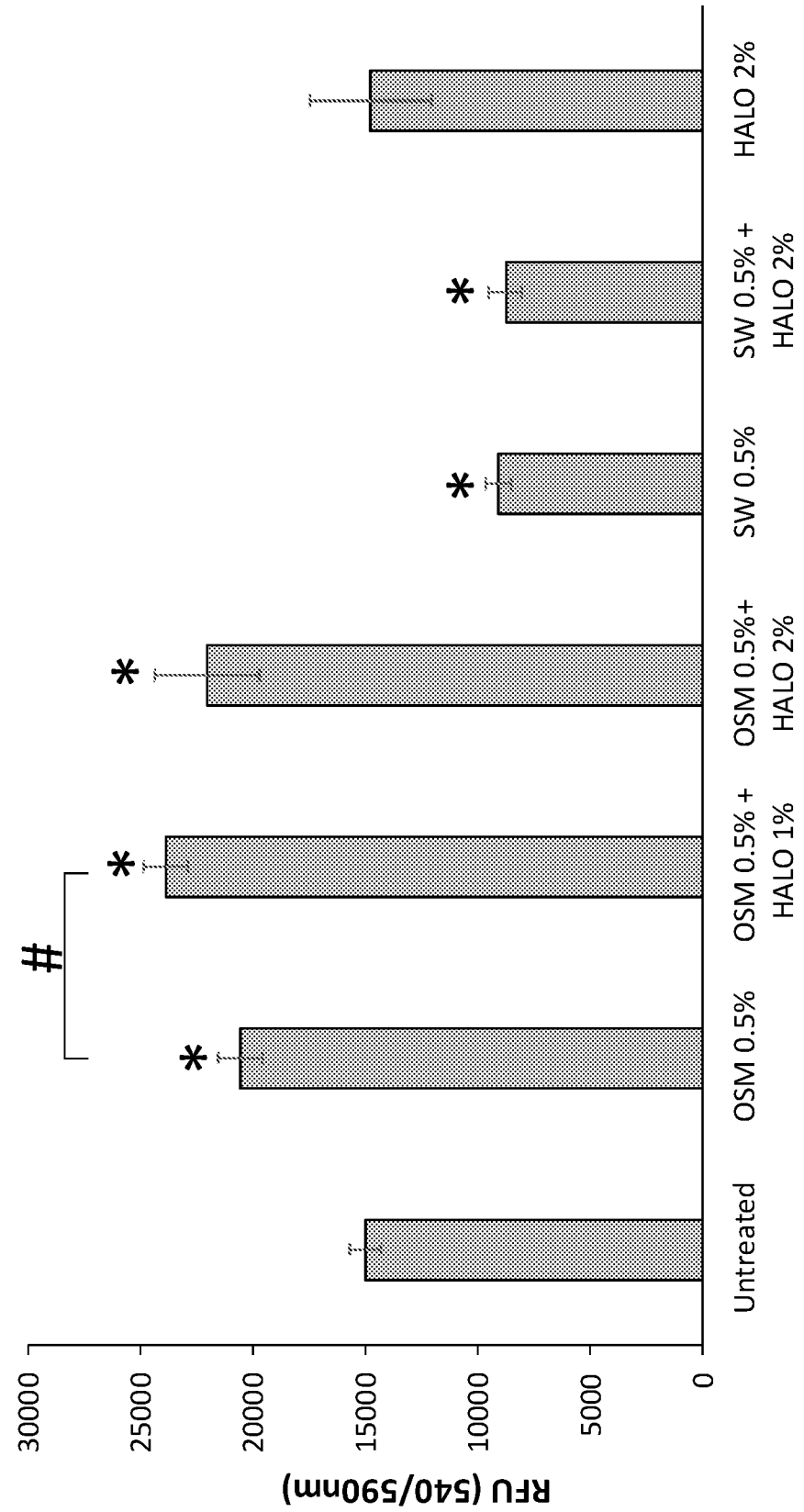

RFU (540/590nm)
30000
25000
20000
15000
10000
5000
0
Untreated
OSM 0.5%
OSM 0.5% + HALO 1%
OSM 0.5%+ HALO 2%
SW 0.5%
SW 0.5% + HALO 2%
HALO 2%
*
*
#
*
*

Figure 2

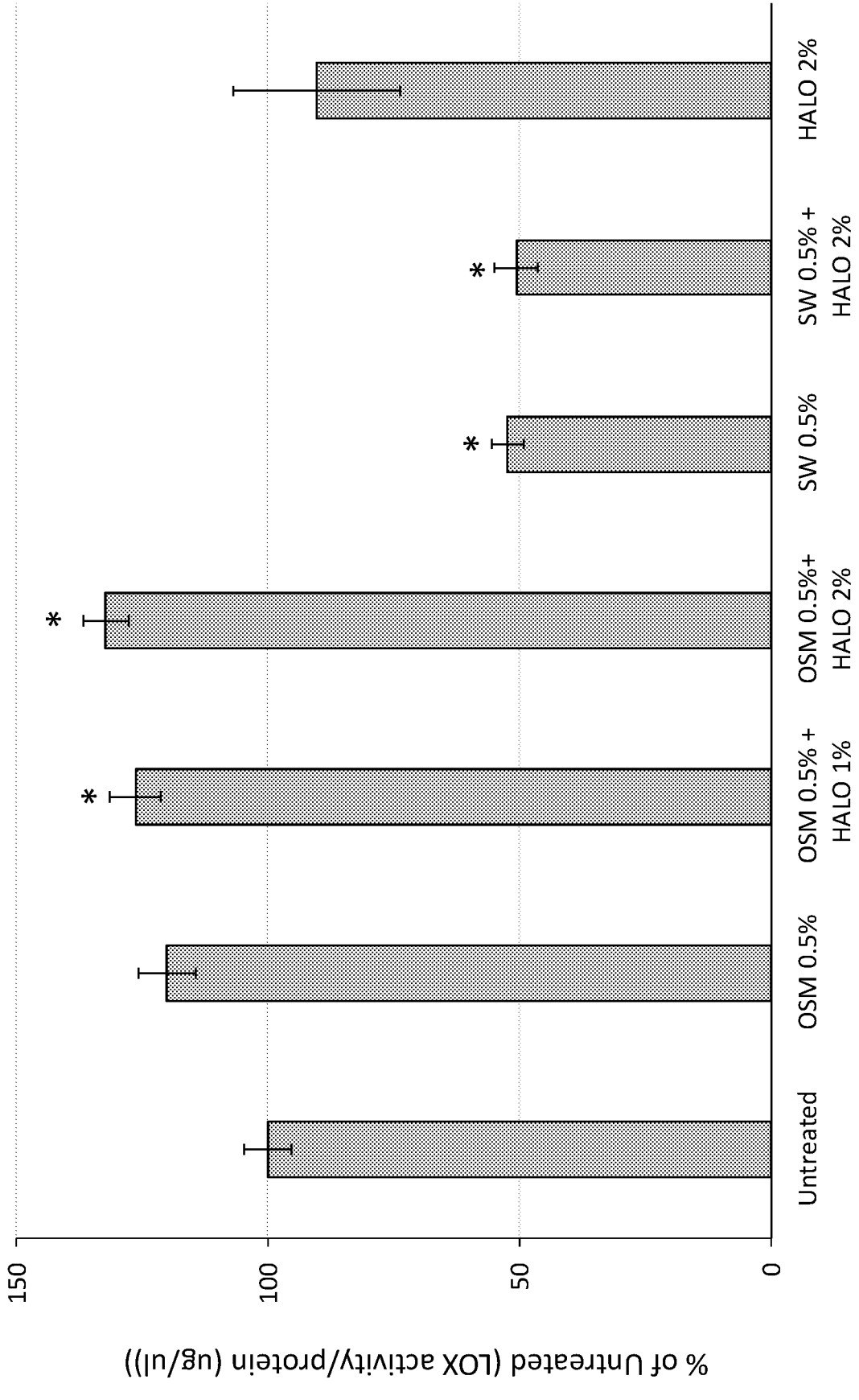

% of Untreated (LOX activity/protein (ug/ul))
150
100
50
0
Untreated
OSM 0.5%
OSM 0.5% + HALO 1%
OSM 0.5%+ HALO 2%
SW 0.5%
SW 0.5% + HALO 2%
HALO 2%
*
*
*

Figure 3

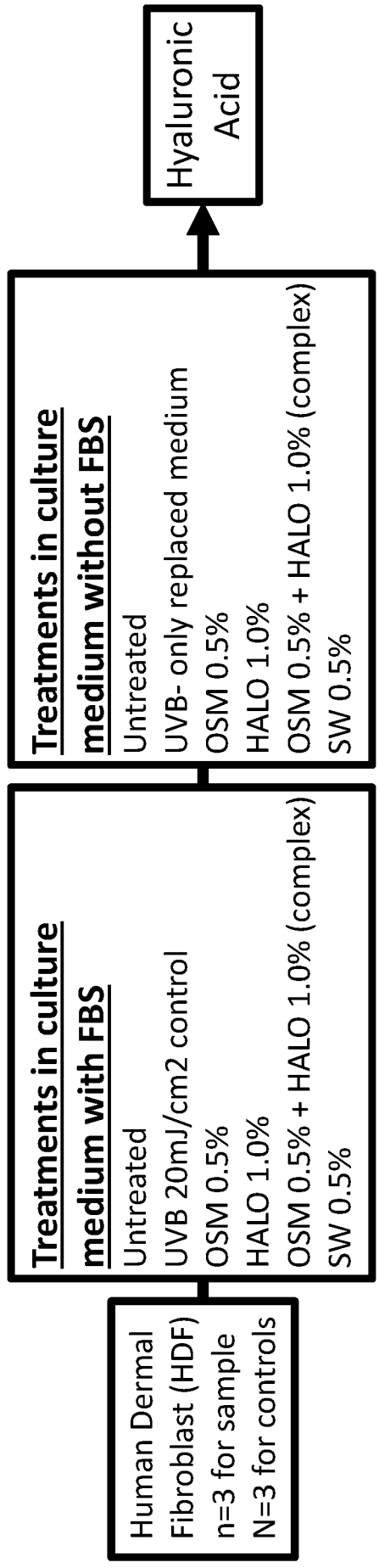

Human Dermal Fibroblast (HDF)
n=3 for sample
N=3 for controls
Treatments in culture medium with FBS
Untreated
UVB 20mJ/cm2 control
OSM 0.5%
HALO 1.0%
OSM 0.5% + HALO 1.0% (complex)
SW 0.5%
Treatments in culture medium without FBS
Untreated
UVB- only replaced medium
OSM 0.5%
HALO 1.0%
OSM 0.5% + HALO 1.0% (complex)
SW 0.5%
Hyaluronic Acid
24 h
24 h

Figure 4

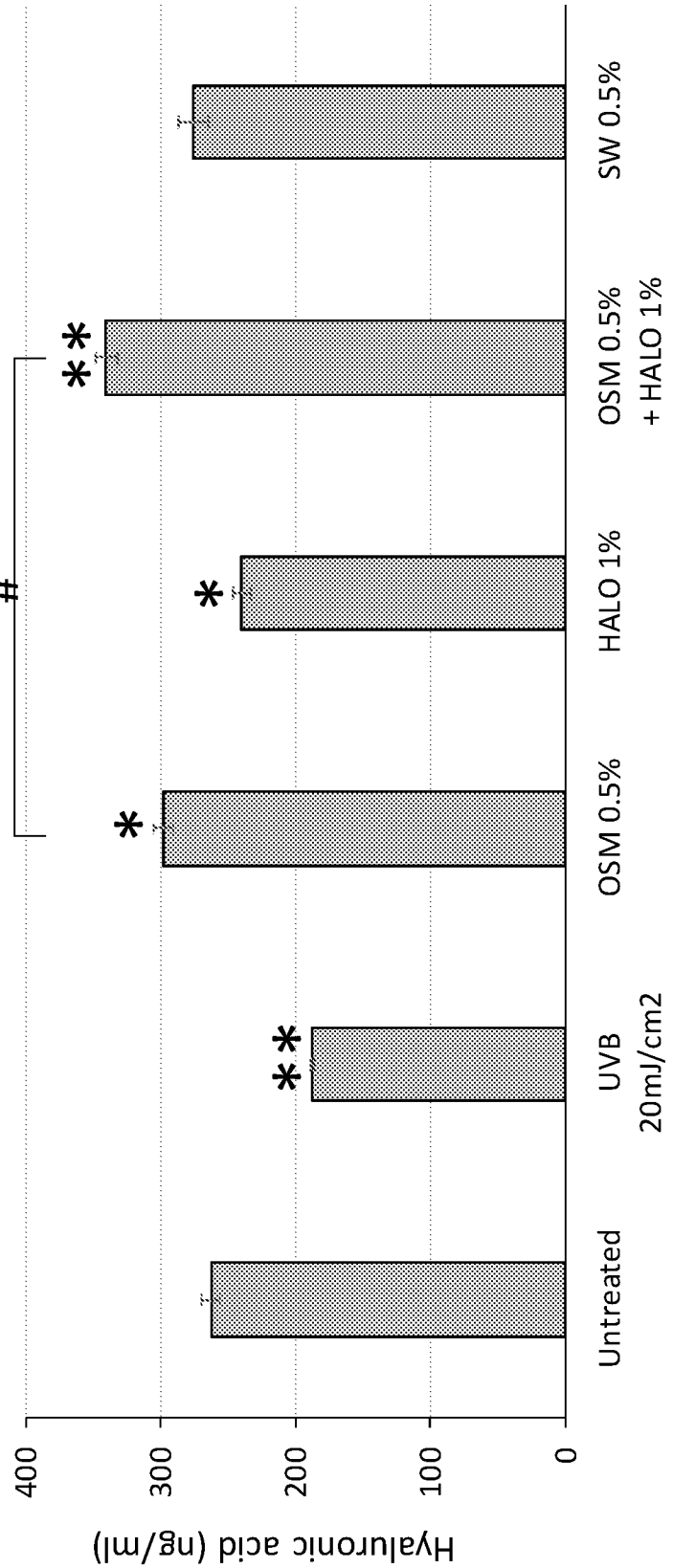

Hyaluronic acid (ng/ml)
400
300
200
100
0
Untreated
UVB 20mJ/cm2
OSM 0.5%
HALO 1%
OSM 0.5% + HALO 1%
SW 0.5%
#
*
**
*
**

Figure 5

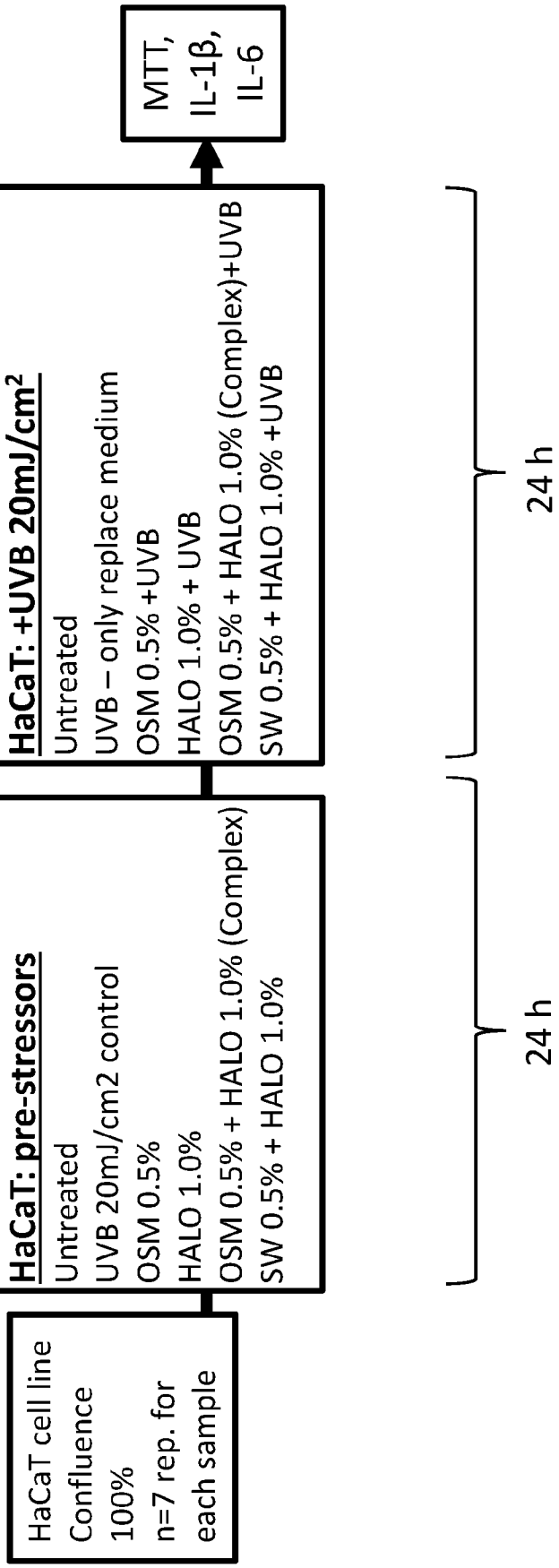

HaCaT cell line
Confluence
100%
n=7 rep. for
each sample
HaCaT: pre-stressors
Untreated
UVB 20mJ/cm2 control
OSM 0.5%
HALO 1.0%
OSM 0.5% + HALO 1.0% (Complex)
SW 0.5% + HALO 1.0%
HaCaT: +UVB 20mJ/cm²
Untreated
UVB – only replace medium
OSM 0.5% +UVB
HALO 1.0% + UVB
OSM 0.5% + HALO 1.0% (Complex)+UVB
SW 0.5% + HALO 1.0% +UVB
MTT,
IL-1β,
IL-6
24 h
24 h

Figure 6

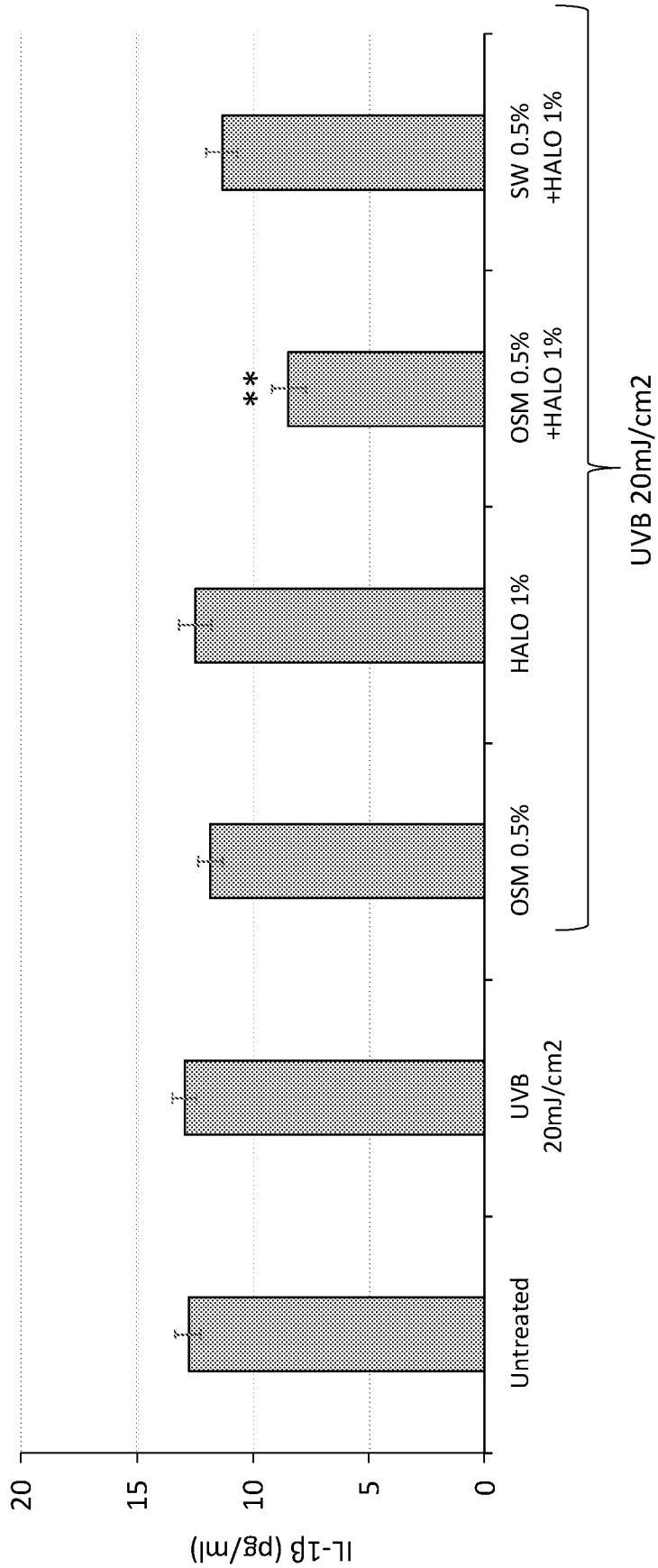

IL-1β (pg/ml)
0
5
10
15
20
**
Untreated
UVB 20mJ/cm2
OSM 0.5%
HALO 1%
OSM 0.5% +HALO 1%
SW 0.5% +HALO 1%
UVB 20mJ/cm2

Figure 7

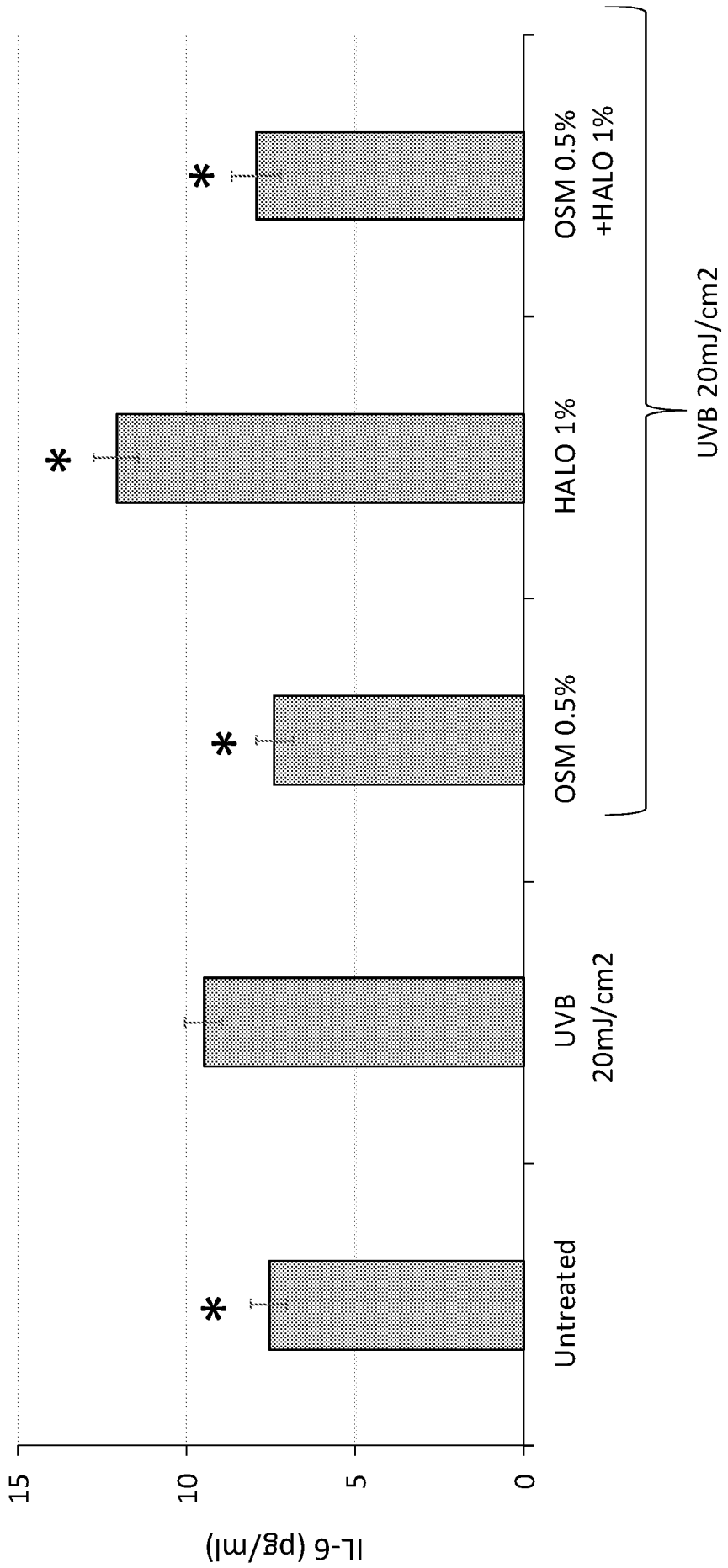

IL-6 (pg/ml)
0
5
10
15
*
*
*
*
Untreated
UVB 20mJ/cm2
OSM 0.5%
HALO 1%
OSM 0.5% +HALO 1%
UVB 20mJ/cm2

Figure 8

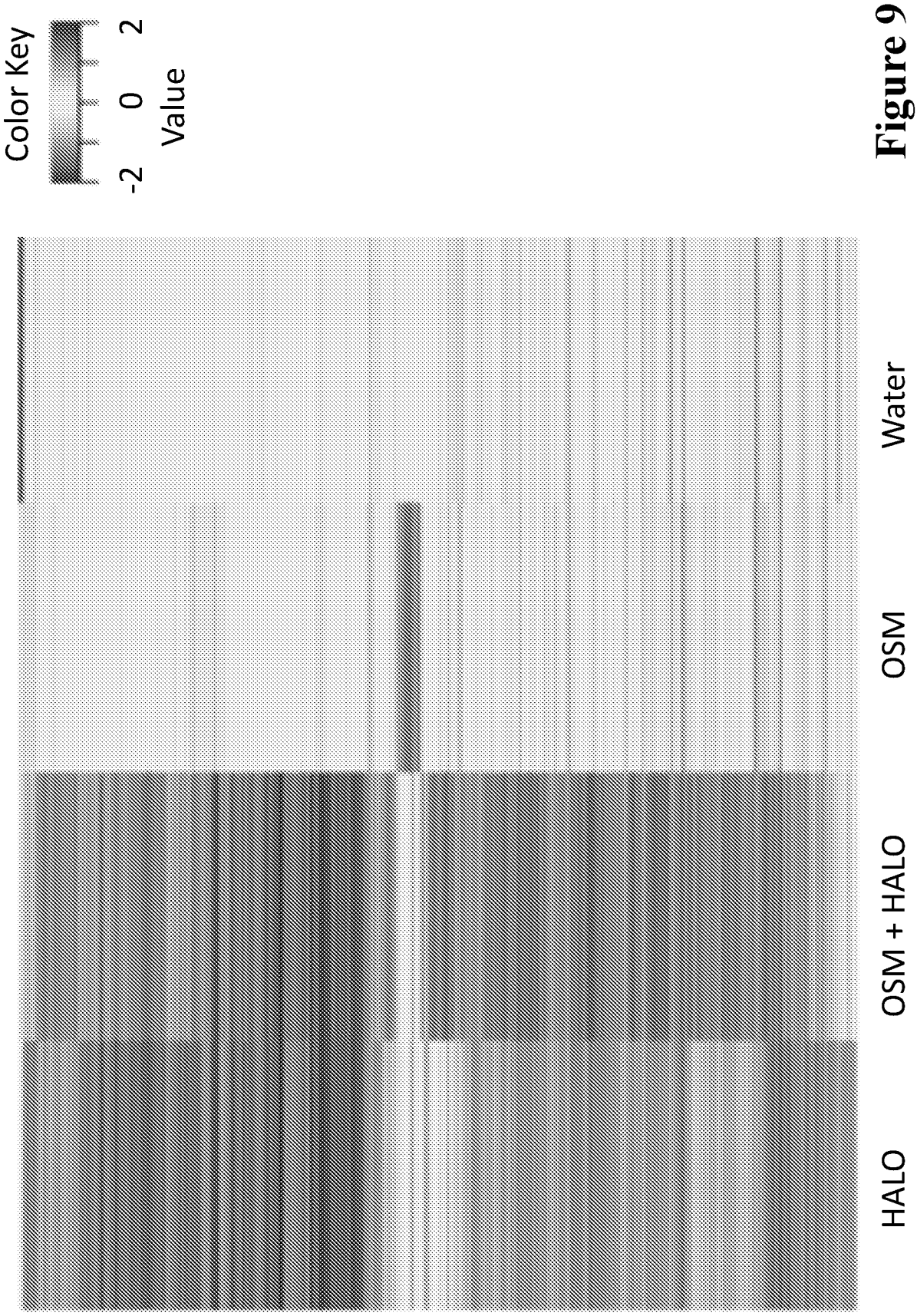


Figure 9

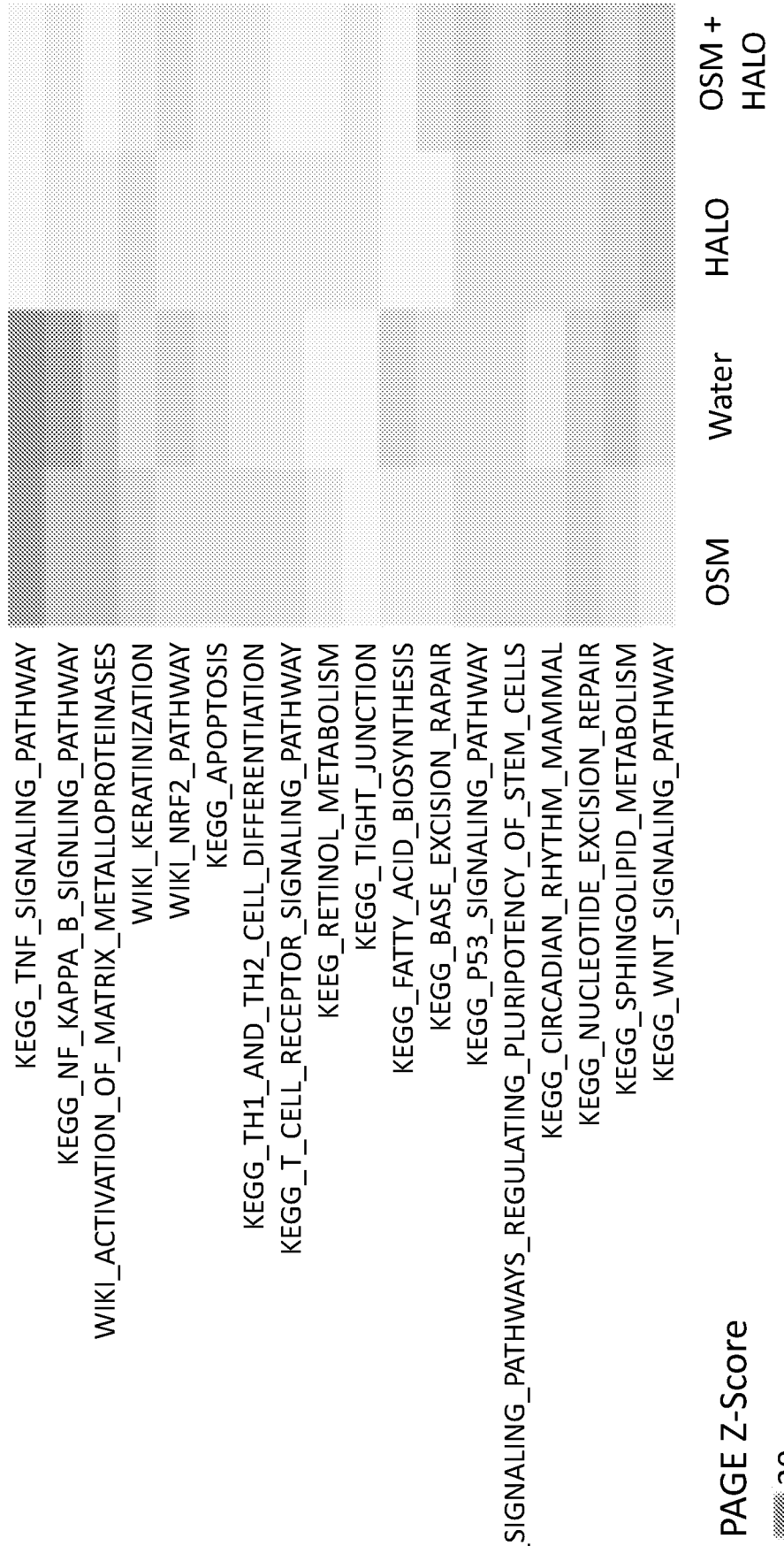

KEGG_TNF_SIGNALING_PATHWAY
KEGG_NF_KAPPA_B_SIGNLING_PATHWAY
WIKI_ACTIVATION_OF_MATRIX_METALLOPROTEINASES
WIKI_KERATINIZATION
WIKI_NRF2_PATHWAY
KEGG_APOPTOSIS
KEGG_TH1_AND_TH2_CELL_DIFFERENTIATION
KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY
KEEG_RETINOL_METABOLISM
KEGG_TIGHT_JUNCTION
KEGG_FATTY_ACID_BIOSYNTHESIS
KEGG_BASE_EXCISION_RAPAIR
KEGG_P53_SIGNALING_PATHWAY
KEGG_SIGNALING_PATHWAYS_REGULATING_PLURIPOTENCY_OF_STEM_CELLS
KEGG_CIRCADIAN_RHYTHM_MAMMAL
KEGG_NUCLEOTIDE_EXCISION_REPAIR
KEGG_SPHINGOLIPID_METABOLISM
KEGG_WNT_SIGNALING_PATHWAY
OSM
Water
HALO
OSM + HALO
PAGE Z-Score
20
10
0
-10
-20

Figure 10

Figure 10 (continued)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2023/050336

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K33/00 A61K8/99 A61K35/74 A61P17/06 A61Q19/00
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)
A61K A61P A61Q

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HENRIET OLIVIER ET AL: "Exploring the diversity of extremely halophilic archaea in food-grade salts", INTERNATIONAL JOURNAL OF FOOD MICROBIOLOGY, ELSEVIER BV, NL, vol. 191, 20 August 2014 (2014-08-20), pages 36-44, XP029077137, ISSN: 0168-1605, DOI: 10.1016/J.IJFOODMICRO.2014.08.019 figures 3,4	1-5

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[x] Further documents are listed in the continuation of Box C.

[x] 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

"E" earlier application or patent but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 May 2023	06/06/2023

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

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International application No
PCT/IL2023/050336

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