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Review

The Biological Role of Dead Sea Water in Skin Health: A Review

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Abstract: Applying natural mineral water to skin care is a popular tendency and many cosmetics products based on thermal spring water have been developed. The special location and environmental conditions provide Dead Sea water (DSW) with unique ion composition and concentrations, which bring comprehensive positive effects on skin health. This article reviews two potential action modes of DSW, and the biological function of DSW and its related complex in dermatology and skin care. Previous studies have proved the functions of skin moisturization, anti-inflammation, skin barrier repair, and anti-pollution. Especially, the anti-aging effect of DSW and related complexes can act in three different ways: keratinocyte rejuvenation, photo-protection, and cellular energy elevation. Additionally, the issues that need further investigation are also discussed. We hope that this review will help to improve the understanding of DSW and its related complex, and further contribute to product development in the skincare industry.

Keywords: Dead Sea; natural mineral water; skin health; cosmetics; molecular mechanism

1. Introduction

The Dead Sea, located on the border of Israel, Palestine, and Jordan, is the lowest point on the continent and one of the three most saline lakes in the world, with a salinity of about 300‰. The extreme environmental conditions have shaped the Dead Sea into a forbidden area for higher plants and animals. Only a few salt-tolerant plants and microorganisms can survive on the shore or around the lake. Nevertheless, the skincare benefits of Dead Sea water (DSW) have been known since biblical times [1], mainly due to its unique ionic concentration and composition.

Compared to other natural waters, such as ordinary seawater and hot springs, DSW has a very high ratio of divalent to monovalent cation concentrations. The main divalent cations are magnesium, calcium, and strontium, and the main monovalent cations are sodium and potassium. Additionally, the highest concentration of anions is not chloride ion, but bromine ion, and DSW also contain some trace metal elements, such as zinc and manganese. The elemental composition of DSW is shown in Table 1.

Numerous experimental and cohort studies have proved the therapeutic properties of DSW in dermatological conditions. Therapeutic bathing in the Dead Sea can significantly improve skin dryness, peeling, itching, and pain, and alleviate the related inflammation [2]. All these are the common symptoms caused by chronic skin diseases, such as psoriasis, atopic dermatitis, seborrheic dermatitis, and vitiligo [3]. Therefore, Dead Sea climate therapy has become a recognized adjunctive treatment for skin diseases recommended by dermatologists [4]. Thanks to these properties, scientists endeavored to investigate the skincare benefits and potential cosmetics application of DSW through both in vitro and in vivo evaluations. The results showed that DSW and related complexes can protect the skin comprehensively via moisturization, barrier repair, anti-inflammation, and anti-aging.

This review is aimed to summarize the reports on the mechanism of action, the skincare properties of the DSW and its related complex, as well as research directions in the future.

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Table 1. Major elements composition in Dead Sea water.

Main Elements	Name	Dead Sea Water (mg/L)
Na^+	Sodium	2295
K^+	Potassium	1440
Ca^{2+}	Calcium	27,620
Mg^{2+}	Magnesium	67,120
Sr^{2+}	Strontium	516
Cl^-	Chlorine	2300
Br^-	Bromine	38,000
SiO_2	Silicate	<20
Li^+	Lithium	30
Mn^{2+}	Manganese	6
Zn^{2+}	Zinc	≤2

2. Mechanism of Action of DSW

2.1. Direct Action

There is a long history of trying to incorporate or directly use mineral-rich water for skin care. Massive scientific studies have proved the positive skin conditioning effect as a result of the different types, concentrations, and ratios of mineral elements [5]. For example, using hairless mice as experimental subjects, the scientist found that applying magnesium chloride solution alone can accelerate skin barrier restoration [6]. The exocytosis function of lipid-containing platelet vesicles within upper epidermal keratinocytes was elevated after using chloride ion carriers [7]. Another experiment found that the application of K^+ channel blockers inhibited skin recovery, whereas treatment with molecules that open the same channels (or are classified as K^+ carriers) can accelerate skin recovery by regulating platelet vesicle secretion. This suggested that the alterations of K^+ channel activity can significantly affect skin barrier homeostasis [8]. Moreover, Ca^{2+} gradient and signaling are also key for a healthy skin barrier and barrier homeostasis. During aging, as well as in diabetic skin, dysregulated calcium signaling occurs and the Ca^{2+} gradient is flattened [9]. Besides driving keratinocyte differentiation, the Ca^{2+} gradient also plays a role in cell migration and wound healing [10]. In summary, it can be assumed that the abundance of Mg^{2+}, Ca^{2+}, Cl^-, and K^+ in DSW can prominently improve the barrier function of the skin. At the same time, the experiment has revealed that the application of 5% $MgCl_2$ can specifically inhibit the TNF-α production by epidermal cells, and also the antigen-presenting capacity of Langerhans cells [11]. Due to the high concentration of Mg^{2+} in DSW, we can conclude that DSW has good anti-inflammation potential.

In addition to different types of elements, the concentrations and ratios of elements can also impose various effects on skin health. For example, Avène Thermal Spring Water, which is low in minerals but rich in bicarbonate and silicates, could serve as a regulator for cell membrane fluidity, antioxidants, and an anti-inflammatory agent [12,13]. Oppositely, the mineral-rich Vichy Thermal Spring Water exhibited more diverse skincare effects, including the increase of stratum corneum peroxidase activity and the promotion of skin homeostasis-related gene expression [14,15]. Thus the unique ionic composition and ratio in DSW may also confer powerful potential for skin care applications.

2.2. Indirect Action

In previous research, Ca^{2+}, due to its high inspecting sensitivity, was selected as the biomarker to represent the ion transport in DSW. No change was observed in the calcium concentration of the culture medium, which suggests that the ions in DSW might not function via transdermal transport [16]. Moderate ionic osmotic stress (MIOS), induced by applying hypersaline materials like Dead Sea water and mud, has been proven to have beneficial contributions to skin health. The positive effects include an impact on the modulation of cell-cycle dynamics, which further leads to a stronger epidermal barrier function, skin hydration elevation, and inflammatory response reduction [17]. The fundamental

principle is that the dissolved mineral salts act through the induction of the cell osmosis, and participate in osmotic stress mechano-transduction via piezo-electric ion channels [18].

Although these conclusions have been proven by many experiments at the molecular level, the fundamental mechanism remains unknown. To verify the conjecture, Cohen et al. performed experiments on internal ROS-elevated skin cells and organ models. They found that enhanced Nrf2 (nuclear factor erythroid-2- related factor 2) translocation into the nucleus, upregulation of phase-II antioxidant enzymes, and downregulation of NF-κB-related inflammatory proteins (cytokines IL-1β, IL-8, and caspase-3) are witnessed after MIOS exposure. Taken together, MIOS can result in modulating intracellular ROS generation, which activates the physiological redox homeostasis of the skin and evokes the induction of various biochemical pathways, such as the Nrf2 pathway [19].

3. Biological Function of DSW and Related Complexes (Figure 1)

3.1. Dermatological Treatment

Atopic dermatitis, psoriasis, vitiligo, ichthyosis, and granuloma annulare, are typical chronic skin diseases with a high rate of relapse [20]. The treatment of these diseases often involves the topical use of drugs, such as corticosteroids, antihistamines, immunomodulators, and antibacterial agents, which can lead to great side effects and drug dependence [21]. Dead Sea climatotherapy, as an effective, cost-effective, and safer method, has been consolidated in many studies for its therapeutic efficacy [22,23].

In 2000, Elkayam et al. conducted Dead Sea climatotherapy (DSC) in psoriatic arthritis patients [24]. Within four weeks, several clinical indicators were measured by dermatologists at regular intervals to evaluate the efficacy. PASI (Psoriasis Area and Severity Index), patient self-assessment, and the Schober test showed statistically significant improvements after treatment. These variables are valid and reliable in psoriatic arthritis severity definition [25,26]. The cohort study of 1718 patients with atopic dermatitis showed that over 95% clearance could be achieved in 4 weeks and more after DSC [27]. Also, DSW-containing cream has been demonstrated to improve skin parameters associated with atopic dermatitis in children, particularly in transepidermal water loss (TEWL) and objective severity assessment of atopic dermatitis (OSAAD) values [28].

TEWL measurement is widely used to assess skin barrier function [29] and has a significant correlation with the clinical severity of chronic dermatosis [30]. Plaque psoriasis is the most common form of psoriasis and its treatment effect can be partly reflected by the PASI value. Harari et al. found a positive effect on PASI after DSC, particularly in the early stages of the disease [31]. Previous studies have also revealed increased levels of encephalin, an opioid peptide known to modulate inflammatory responses and keratinocyte proliferation, in psoriatic skin tissues [32]. After four-week DSC treatments, the clinical symptoms of patients disappeared and enkephalin levels in keratinocytes decreased by 21% [33]. Meanwhile, the mean SCORAD (atopic dermatitis score) value was found to decrease from 50.5 to 11 after around 30-day DSC treatments [34]. The potential therapeutic effect of DSC on vitiligo was also confirmed by analyzing the clinical statistical parameters of 436 patients. At the end of treatment, more than 80% of the patients showed improved repigmentation, which was better than the typical narrow-band ultraviolet B treatment [35]. DSC treatment in psoriasis disease can not only bring immediate alleviation but also exert a long-lasting effect [36]. Also, human trials suggested that the mean PASI decreased from 31.7 to 1.42 after the four-week DSC treatment with an improvement of 95.5%. All patients achieved PASI 50, which was thought to be a clinically meaningful improvement and primary endpoint in psoriasis [37], and the therapeutic effect can last up to 33.6 weeks [38]. These results together revealed the good applicate potential of DSW in chronic skin disease treatment.

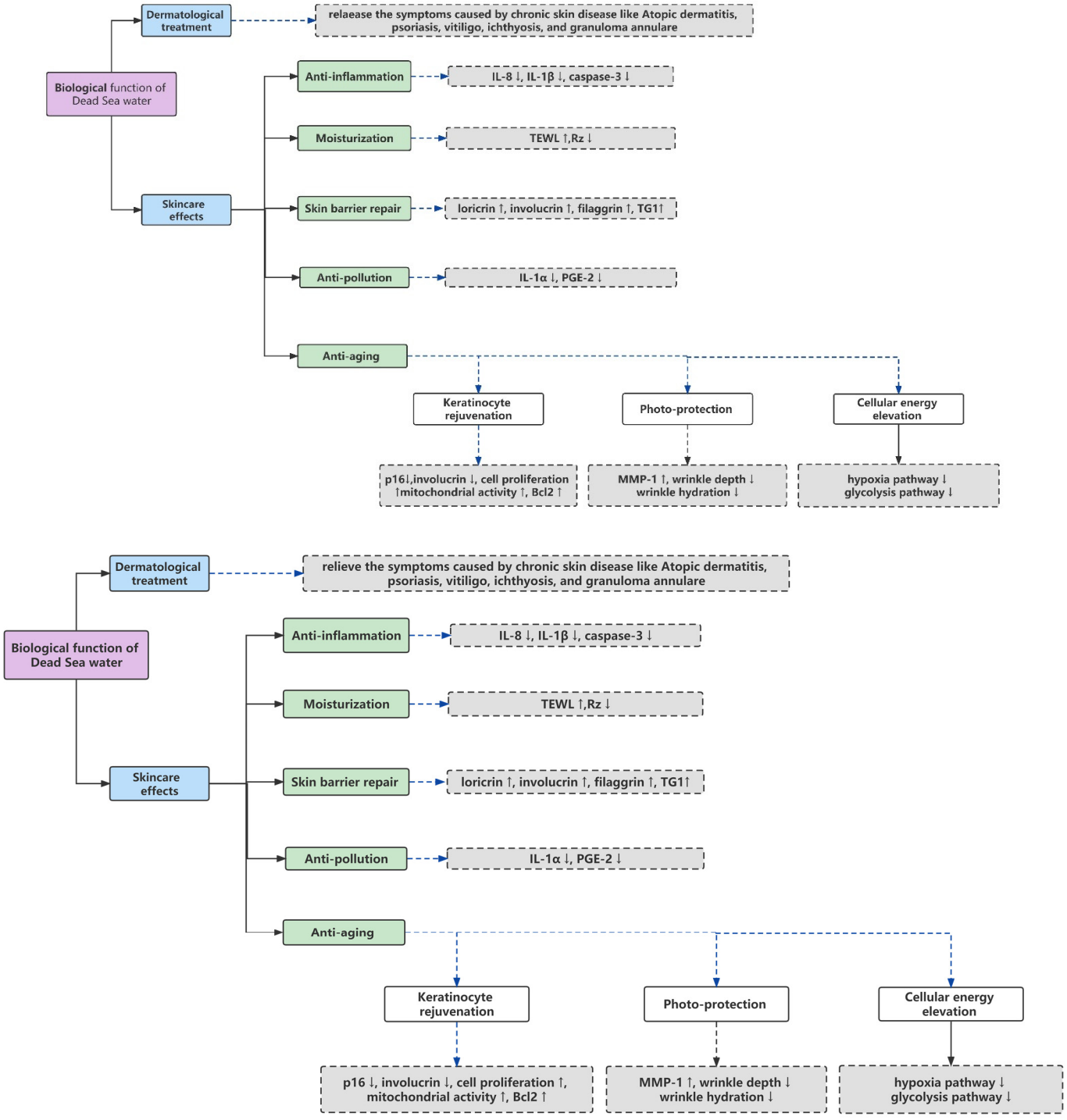

Figure 1. Overview of the biological function of Dead Sea water in dermatology and skin care.

3.2. Skincare Effects

3.2.1. Moisturization

To clarify the effect of bathing in DSW, especially the biophysical characteristics in atopic dry skin, transepidermal water loss (TEWL), skin hydration, skin roughness, and skin redness were measured. Eitan et al. compared the indexes before the study and at weeks 1–6, then they observed the elevation of basal TEWL and enhanced skin hydration. Meanwhile, the common skin inflammation markers, such as roughness and redness, were also significantly reduced after treatment [39]. By evaluating skin roughness using computer-aided laser profilometry, Ma'Or et al. investigated the cutaneous smoothing

effects of three different liquid gels, one of which contained Dead Sea minerals. After four weeks, the gel containing 1% Dead Sea mineral solution reduced skin roughness by 40.7%, which boosted a better moisturizing effect than the other two gels [40].

In addition, the complexes that combine DSW with other active substances also exhibits good moisturizing properties. Triple D Complex^{TM}, the mixture of DSW, *Dunaliella salina* algae extract, and desert plants, was developed and added into a cosmetic cream. *Dunaliella salina*, a unicellular halophilic microalga with a red colony, is the commercialized producer of many compounds within the carotenoid family. Its extract showed good antiglycation, anti-aging, and anti-inflammatory capabilities in the ex vivo human skin explants model [41,42]. After four-week treatments, they found an average reduction of the skin roughness parameter Rz by 43%, which is measured by the silicone impression. The skin surface hydration state was also assessed by a corneometer (a skin capacitance-based instrument) and the appearance improvement was also observed after application [43].

3.2.2. Anti-Inflammation

Cohen et al. used UVB irradiation-induced skin explant as the model and co-cultured it with the DSW. A downregulated level of interleukins secretion levels, such as IL-8 and IL-1β, as well as a lower level of caspase-3 proapoptotic enzyme, were observed after DSW treatment [19]. Furthermore, Portugal-Cohen et al. also constructed another inflammation-induced model by lipopolysaccharides (LPS) on Human skin organ culture. They found that treatment with DSW at concentrations of 0.1% and 0.5% can significantly attenuate IL-1β induction by 46% and 54%, respectively [16]. From the in vitro tests, it is obvious that DSW exerts inflammation inhibition ability.

Clinically, the DSW also demonstrated an anti-inflammation effect on chronic inflammatory skin diseases, such as psoriasis or atopic dermatitis. As reported by Proksch [39], a magnesium-rich Dead Sea salt solution was applied to patients with atopic dry skin. A 15 min treatment in bath solution containing 5% Dead Sea salt for 6 weeks could greatly improve skin hydration, roughness, and reduce skin redness. It was proposed that the anti-inflammatory property of the DSW might originate from the modulation of interleukins, as well as the antigen-presenting capacity of Langerhans' cells [44].

Magnesium in DSW might contribute the most to inflammation inhibition. DSW is known for the abundance of magnesium ions. As summarized by Tarnowska [45], magnesium could reduce TNF-α production in epidermal cells, thus bringing skin soothing effects. Additionally, magnesium-rich Dead Sea therapy has been proven to downregulate nuclear factor κB (NFκB) to avoid further inducement of proinflammatory factors and integrin. In Kim's study [46], a Korean Sea derivative with similar mineral composition showed similar anti-inflammatory properties, consolidating the hypothesis that magnesium-enriched seawater has a protective effect against skin inflammation from different sources.

3.2.3. Skin Barrier Repair

Skin, as the largest organ in the human body, forms the first barrier against different exogenous stress, performing a barrier function maintenance in skin homeostasis. To clarify the internal mechanism, four barrier function-related proteins: loricrin, involucrin, filaggrin, and transglutaminase 1 (TG1), were measured on skin equivalents after applying DSW at concentrations of 0.8% and 2% [16]. The results suggested that the latter three structural-related biomarkers were upregulated after topical DSW application. Involucrin is thought to be one of the precursors cross-linked during the resistant cornified envelope assembly process, which is partly driven by TG1 [47]. Filaggrin is another important protein during the final stages of keratinocyte differentiation, which can promote keratin filaments aggregation and further form into tight bundles [48]. Further tests on SDS-induced (sodium dodecyl sulfate) human skin irritation organ culture (HSOC) showed that topical DSW application alleviated the reduced epidermal viability and decreased IL-1α and PGE2 levels, which are in line with previous reports of skin response to minerals in animal models. DSW

can also attenuate LPS-induced IL-1β secretion, which is probably related to its skin barrier-restoring effect. The complete skin barrier can prevent skin from the harmful stimulation of the external environment, and from the release of inflammatory markers, such as cytokine and PGE [49]. Former research has found that osmotic pressure can stimulate TRPV4, an important signal molecule in the regulation of calcium gradient and barrier homeostasis in the epidermis [50]. Considering the central role of Ca^{2+} in epidermic protein synthesis and its high concentration in DSW, it can be conjectured that DSW might function in two parallel ways, namely the mediation of TRPV4 and the calcium-pump activation by osmotic pressure, thus regulating the expression and activity of the epidermal-related protein.

3.2.4. Anti-Pollution

With the increasing deterioration of the natural environment, the negative skin impact of air pollution attracts the attention of dermatologists [51]. In a recent study, the common pollution models, ozone and a mixture of pollutants (MOP) composed of heavy metal and atmospheric particulate matter [52], were selected to induce the oxidatively-stressed state in 3D skin cell culture. Using epidermal viability and inflammatory biomarkers as the indicator of effect, it was found that DSW can inhibit the IL-1α overproduction following MOP exposure. When mixed with another active ingredient, for example, anionic polysaccharide PolluStop® (bio-saccharide gum-4 or 1,2-hexanediol), the release of IL-1α and PGE-2 induced by ozone exposure can be further reduced [53].

3.2.5. Anti-Aging

Keratinocyte Rejuvenation

Skin aging often leads to increased wrinkles, decreased elasticity, and reduced skin thickness [54]. These phenotypes can not only bring a negative appearance but also deteriorate the individual's confidence. Accordingly, the anti-aging function of DSW was studied and verified by a series of lab experiments. First, the researchers developed the biological model of aged epidermal keratinocytes by characterizing the cellular and molecular properties, including the morphological, fluorometric, and biochemical parameters on both skin cell and organ cultures [55]. Then, the altered expression of 16 biochemical molecules in both aged cultured cells and tissues was observed and selected as the aging biomarkers, including caspases-1 and 3, beta-galactosidases, p16, Ki67, 20S proteasome, and effectors of the Fas-dependent apoptotic pathway [56]. After applying DSW to both models, they found that mitochondrial activity and cell proliferation are increased at subtoxic doses. The DSW treatment group also showed significantly reduced p16 and involucrin signals and increased Bcl2 levels, as observed in non-senescent cells. A possible explanation is that DSW can eliminate poorly proliferative and aged cells, to increase the activity of the whole keratinocyte population. In summary, DSW can stimulate proliferation and mitochondrial activity, decrease the expression of aging biomarkers, and limit apoptotic damage after UVB irradiation.

Apart from the use of pure DSW, a combination of DSW and traditional anti-aging actives may present a synergistic effect. Retinol is a commonly-employed ingredient to improve age-related skin issues, but its safety profile is controversial. The scientists designed a new complex named "pRetinolTM" (PRE), which contains β-carotene, niacinamide, the extract of *Dunaliella salina*, and DSW. The former two can serve as the precursors to synthesizing retinol [57]. The extract of *Dunaliella salina* alga has been proven to contain multiple anti-antioxidant substances, which include fatty acids and pigments, such as β-carotene and chlorophyll. The biological function of this complex was evaluated and compared with retinol only by using three different models: in vitro human dermal fibroblasts cell, reconstructed 3D skin equivalent, and ex vivo human skin organ culture. The measurement of hyaluronic acid, TNF-α, and IL-1α expression levels revealed it is of retinol-like skin activity, yet it led to less skin irritation. The whole-genome microarray was also performed to compare the different expression pathways between PRE complex and retinol treatment. The enrichment analysis showed that PRE can reduce many pathways involving inflam-

mation, such as NOD-like receptor signaling [58], TNF signaling, nuclear factor-kappa B (NF-κB) signaling [59], and apoptosis. The complex can additionally up-regulate the BASE excision repair-related gene expression. As an important part of the oxidative DNA damage defense mechanism [60], this complex might provide a protective effect on retinol, which has side effects and toxicity [61].

Photo-Protection

Among the multiple exogenous sources that can result in skin photo-damage and aging, UV exposure is the most important and well-known factor [62]. A mixture of DSW and three plants (Tibetan goji berry, Himalayan raspberry root extract, and Iceland moss (lichen)), namely Extreme Complex^{TM}, was developed in the previous report [63]. The UVB-induced ex vivo human skin model was reconstructed and used to assess its protection function against light radiation. A reduced caspase-3 activity and pro-inflammatory cytokine TNF-α secretion were shown, which suggested its anti-apoptotic and anti-inflammatory functions [64]. Additionally, the complex can also decrease the activity of collagen balance-related biomarkers, degrading enzymes, and collagen maturation byproducts. Within the matrix metalloproteinase (MMP) family, MMP-1 is the most injured enzyme in collagen damage when facing photoaging [65]. MMP-1 activation can further induce the increased expression level of MMP-3 and MMP-9, accelerating collagen degradation [66]. In clinical tests on human subjects, skin wrinkle depth and hydration were common metrics that can reflect the degree of skin photoaging, which can be measured using the PRIMOS optical 3D measuring device and corneometer, respectively [67]. A significant improvement in skin moisture and wrinkle depth is observed after application. Altogether, the antioxidant, anti-apoptotic, and anti-inflammatory characteristics of this complex might bring comprehensive alleviation effects of skin photo-damage and appearance improvement.

Under certain conditions, adding metal ions into the fermentation medium has been proven to improve the structure and function of products [68]. Since Dead Sea water is rich in minerals and trace elements, scientists developed a fermentation supplement by mixing the water and mud of the Dead Sea, which acts as a positive stress supplement during yeast Pichia pastoris (aka *Komagataella phaffii*) fermentation. This kind of methylotrophic microorganism is one of the most commonly used cell factories for heterologous protein production and has been used in many industries [69]. To evaluate the biological functions of this complex, Portugal-Cohen et al. first measured a series of skin elasticity biomarkers on 3D human skin equivalents and performed the whole-genome DNA microarray test at the same time, to investigate its effect on both gene and protein levels, respectively [70]. After treatment, the experimental group had significant alleviation of abnormal UVB-induced alterations; for example, both elastin and fibulin are the main components of the extracellular matrix, which is the damage target of UV solar [71]. Tight junction protein (TJ) can connect multiple parallel intramembrane strands and neighboring cells into a regulatory and structural network [72], which can contribute to the skin's UV resistance capacity [73]. The elevation of these proteins indicates the skincare potential of this complex.

The UV-protection effect of DSW is also consolidated in DSW-containing cosmetic creams [74]. A cream composed of DSW, zinc oxide, aloe vera extract, pro-vitamin B5, and vitamin E, was formulated and topically applied to human skin organ cultures exposed to UVB. A severe mitochondrial activity loss was observed after UV radiation, as activated by caspase-3 and cytokine secretion, which was well accorded with previous studies [75]. On the contrary, the DSW-incorporated formulation significantly promoted the anti-oxidative capacity and reduced cell damage and apoptosis. It was inferred that the DSW could minimize oxidative stress and inflammatory signs after UV exposure.

Cellular Energy Elevation

Organisms that live in extreme environments usually evolved many special mechanisms for survival [76]. *Calotropis procera*, the traditional American medicinal plant, naturally grows in the flora of the Dead Sea region [77]. The previous study has found

many pharmacological actions of its extracts, such as anti-inflammatory, antibacterial, and antioxidant [78]. After mixing with DSW, various biological activities are further amplified and enhanced, which was verified by the RNA microarray experiment on the reconstructed full-thickness skin tissues. The GSEA analysis results showed that the biological processes of hypoxia, glycolysis, and epithelial-mesenchymal transition pathway were significantly down-regulated after treatment. These results indicated that this complex had an unexpected biological potential for energy production, resistance to hypoxia, and ECM balance [79].

4. Current Challenges for the Use of DSW

Though DSW shows a unique biological role in maintaining skin health, there are still tremendous issues to be addressed.

The core problem is how to strike the balance between Dead Sea resources exploitation and eco-protection. Environmental factors, such as climate alteration, ongoing sinkholes, and geochemistry variation, could lead to the scarcity of water resources [80]. In addition to the natural influences, human intervention also threatens the preservation of Dead Sea resources. Water pollution, exhaustive exploitation, and changes in biodiversity could all aggravate the exhaustion of Dead Sea resources. As reported, the Dead Sea's sea level has dropped at a speed of 1 m/year in the last 5 decades, bringing the challenge of sustainable supply of DSW.

The exterior variation of the Dead Sea also contributes to another issue: quality control. Apart from seasonal and locational differentiation, the ion concentration, the ratio between different minerals, and the metabolites from microbials could be affected by environmental changes, which might eventually lead to unpredictable biological effects.

The application of DSW in cosmetic products also evokes great challenges, not only because a higher concentration of DSW in products might cause potential skin irritation and discomfort, but also due to its relatively high ion strength. This would hamper the stability of the cosmetic formula by sabotaging emulsion thermo-dynamic homogeneity and altering the rheological properties of the whole system. Additionally, DSW might also impose an antagonistic effect with other actives in formula, resulting in unwanted precipitation or efficacy invalidation. However, there is a cosmetic brand that has produced a series of related products with broad effects and diverse forms, like hydrating sprays, lotions, and creams. The DSW here functions more as the actives instead of the main ingredient.

Considering this, many efforts have been made to improve their utilization in formulations. For example, scientists dispersed the nanosized Dead Sea mineral in mixed oil (Crystal Osmoter™) and achieved six times higher concentrations DSW on skin, for which the clinical tests showed a better performance on wrinkle reduction, firming, and radiance than normal DSW with no irritation. At the same time, new delivery systems were also developed, like liposomes (LipOsmoter™) or strontium hexaferrite ($SrFe_{12}O_{19}$) nanomagnets, which enhance the safety of DSW and provide a longer-term skincare benefit.

Although there are some inventions about the DSW application in cosmetics products, still many issues need to be explored, like how to complement the synergy of DSW and how to stabilize the system even if added in a high DSW concentration.

Since the DSW is a complex mixture of different minerals and other trace elements, it is of great urgency to determine the exact composition of DSW. Especially for the trace elements, more advanced analytic techniques are needed to quantitatively evaluate their contents. Facing resource shortages and environment pollution, the artificial DSW (ADSW) consisting of the main ion compositions are formulated in labs. Unfortunately, it has shown weaker effects on both cell models and human skin organ cultures than natural DSW (unpublished data). It is probable that the trace element and microbe-secreted bioactive substances can make up part of the skincare effects of natural DSW. Thus a more delicate choice of DSW content should be studied first.

In addition, the interaction between different ions and dose-function relation of DSW should be further investigated. Each type of ion might play complex roles in modulating biological processes and molecular functions on skin, thus DSW might bring even more complicated cellular interplays.

To sum up, the current challenges for the use of DSW lie in the short supply, unpredictable quality variation, compatibility concerns in the formulas, as well as lack of understanding of DSW components and interrelated mechanism.

5. Future Direction

The skincare benefits of Dead Sea water and its related complex have been demonstrated in many studies and cover a wide range of functions, including moisturization, barrier repair, anti-inflammation, anti-aging, photo-protection, cellular energy elevation, and relief of skin disease symptoms. However, several issues are still worthy of further investigation, which are listed below.

Firstly, although the extreme hypersaline environmental conditions of Dead Sea water hamper the growth of higher plants and animals, microorganisms like fungi and bacteria can still survive [81–83]. Extremophiles are often thought to be a huge reservoir of active substances [84]. For example, an extremely salt-tolerant *Bacillus* strain isolated from Dead Sea had significant antibacterial and fungal activity in its aqueous extract. One of them can even resist all the tested bacteria strains [85,86]. *Haloarcula vallismortis* is a kind of halophilic archaeon with reddish colonies [87]. Its extract has a significant anti-inflammatory activity that can resist the DNA damage induced by UV exposure, which suggests its potential for use as a biological or natural sunscreen [88]. Although some Dead Sea source strains have been isolated and purified, studies for their bioactive product utilization are still scarce and need to be further investigated experimentally.

Secondly, the number of skin microbiome-related studies is increasing rapidly in recent years and the relationship between the skin microbiome and skin health is gradually being revealed [89–91]. The effects of DSW and related complexes on skin microbiomes are less evaluated, and most of them are involved in skin diseases. Based on a healthy population, a previous experiment compared the change in the skin microbiome after DSW application [83]. They found that bacterial community diversity is almost constant, while fungal diversity was significantly lower than before, the variation of which is driven primarily by *Malassezia* spp. It's known that the abnormal abundance of *Malassezia* can lead to free radicals release and inflammatory skin issues [92]. The variation pattern of AD (Atopic Dermatitis) patients has also been explored after using DSW. The results show that the unbalance of skin microbial ecology, which occurs at both lesion and non-lesion sites, was significantly attenuated after DSW application [93]. The most significant changes were seen in severe AD, mainly reflected in the relative abundance of *Staphylococcus epidermidis*, *Streptococcus mitis*, and *Micrococcus luteus*. Current studies usually used the high-throughput 16S rRNA or ITS (internally transcribed spacer) amplicon sequencing method, which is of low resolution and limited information availability. A more comprehensive metagenome approach should be established subsequently to obtain more accurate and profound findings [94].

Thirdly, in contrast to the extensive exploration of DSW, the research involved in the skincare effect of Dead Sea mud is rare [2,95–98]. Previous experimental results have proven that both short-term and long-term application of Dead Sea-derived mud has a high safety profile. It causes no damage to skin barrier integrity but has a firming effect instead [99,100]. Furthermore, Dead Sea black mud-derived masks have been shown to accelerate the wound healing process in mice skin by promoting granulation, angiogenesis, and collagen deposition [101]. The mud is also found to inactivate common microorganisms and produced an obvious growth inhibition area, suggesting its significant antibacterial effect [102]. As the seed of Dead Sea minerals, the studies of Dead Sea mud should not be limited to the basic skincare functions, but also more to its applications in cosmetics.

6. Conclusions

Dead Sea water has a unique ion composition and its benefits on skin health have been well-known since ancient times. From previous research, we summarize two potential action modes of DSW. The first one is the direct penetration of mineral ions, and the second one is the moderate ionic osmotic stress mechanism, which can activate the cellular osmotic stress-related pathway via ion channels. The chronic skin disease improvements and comprehensive skincare efficacy of DSW and its related complex are also illustrated. Specifically, they can resist skin senescence from three different perspectives (keratinocyte rejuvenation promotion, photo-protection, and cellar energy elevation), which indicates their strong application potential in anti-aging cosmetics product development. However, many other aspects of the Dead Sea resource are still unknown and need to be studied, such as the Dead Sea mud, secondary metabolites of Dead Sea bacteria and fungi, and also their effects on the skin microbiome.

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