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Review Article

Polydeoxyribonucleotide: A promising skin anti-aging agent

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ABSTRACT

Polydeoxyribonucleotide (PDRN) consists of DNA fragments with molecular weights ranging from 50 to 1 500 kDa, which are mainly extracted from the sperm cells of salmon trout or chum salmon. Many preclinical and clinical studies have demonstrated the properties of PDRN. These include anti-inflammatory, anti-apoptotic, anti-osteoporotic, anti-melanogenetic, anti-allodynic, anti-osteonecrotic, bone regenerative, tissue damage preventive, anti-ulcerative, and wound healing properties, which are mediated by the activation of the adenosine A_{2A} receptor and salvage pathways. Moreover, PDRN promotes angiogenesis, cellular activity, collagen synthesis, soft tissue regeneration, and skin priming and revitalization and can be used to treat hyperpigmentation. Therefore, this review assessed the potential use of PDRN as an anti-aging agent for the skin.

1. Introduction

Skin aging is an inevitable process driven by two overlapping factors, intrinsic and extrinsic, both of which decrease the structural integrity and physiological function of the skin.[1,2] The human integument serves as a barrier; it separates the body from the outside world and is thus subjected to more insults than most organs. Fine lines, wrinkles, sagging, and dehydrated skin are the first visible signs of aging. Fighting against aging is one of the main challenges of this century. Traditionally, facial rejuvenation involves surgical resection of the sagging skin. In recent years, there has been a major paradigm shift towards the use of minimally invasive therapies.[3] These include daily skincare, use of topical agents, chemical peelings, lasers, injectable rejuvenation, botulinum toxin, and soft tissue augmentation using dermal fillers.[4] The mainspring of each therapy is to achieve healthier, younger-looking skin. A recent report published by the American Society of Aesthetic Plastic Surgery (ASAPS) revealed that the use of dermal fillers is the second most common non-surgical procedure currently performed.[5] Fillers can strive to make the appearance of facial wrinkles and sunken regions less noticeable through soft tissue augmentation, but they play little to no role in the actual anti-aging process. It has been reported that, while existing filler products simply fill the contracted or depressed spaces, polynucleotide-containing products not only fill the space but improve tissue regeneration in the damaged tissue environment, resulting in a more natural tissue regeneration.[1,4] Polydeoxyribonucleotide (PDRN) consists of DNA fragments derived from the sperm cells of *Oncorhynchus mykiss* (salmon trout) or *Oncorhynchus keta* (chum salmon).[6] The chemical structure of PDRN consists of low molecular weight DNA ranging from 50 to 1 500 kDa. It is composed of a linear polymer of deoxyribonucleotides with phosphodiester linkages in which the monomer units are represented by purine and pyrimidine nucleotides. These polymer chains create a double helix-shaped steric structure. The extraction and purification processes allow for the recovery of more than 95% of pure substance. This is important for guaranteeing the absolute absence of immunological reactions. Spermatozoa are the most suitable source for the extraction of highly purified DNA without the risk of impurities, such as peptides, proteins, and lipids.[6] The introduction of PDRN in clinical practice is not new and its astonishing therapeutic effects include anti-inflammatory, anti-apoptotic, anti-osteoporotic, anti-melanogenetic, anti-allodynic, anti-osteonecrotic, bone regenerative, tissue damage preventive, anti-ulcerative, wound healing, and scar preventive effects (Fig. 1).[7–16]

Owing to its properties with regards to angiogenesis, cell activity promotion, collagen synthesis, anti-inflammation, hyperpigmentation treatment, soft tissue regeneration, and skin priming and revitalization and its anti-aging effect, PDRN has revealed its potential as a promising skin anti-aging agent (Fig. 2). Therefore, the aim of this study was to review the skin anti-aging properties of PDRN and its clinical use in the cosmetic industry.

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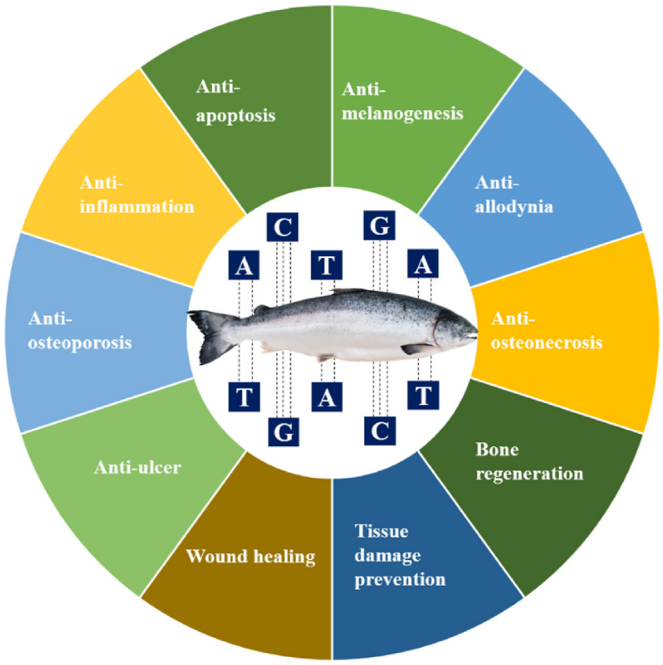

Fig. 1. Therapeutic effects of PDRN. PDRN, Polydeoxyribonucleotide.

2. Mechanism of skin aging

2.1. Intrinsic and extrinsic aging

The mechanisms underlying skin aging can be classified into two types: intrinsic and extrinsic. Reactive oxygen species (ROS) are continuously produced as a by-product of the mitochondrial aerobic metabolism electron transport chain and are considered the main cause of intrinsic aging. The intrinsic aging process due to ROS reduces the number of dermal fibroblasts, increases the expression of matrix metalloproteinases (MMPs), and decreases the ability of the extracellular matrix (ECM) to synthesize collagen and elastin.[17] Extrinsic skin aging mainly results from a prolonged exposure to ultraviolet (UV) radiation, which induces the production of ROS that cause destructive oxidative stress, activate the arachidonic acid pathway, and mediate inflammatory responses.[18–20] The effects of prolonged exposure are age spots, collagen disorder, and even malignant tumors.[19,21,22] The outcome of both the intrinsic and extrinsic factors is the decline in the structural integrity and physiological function of the skin.[2]

2.2. Role of reactive oxygen species

ROS, an unavoidable consequence of aerobic metabolism in the mitochondrial electron transport chain, are a major cause of skin aging.[23] Although the presence of small amounts of ROS exerts beneficial effects in maintaining the health of cells, ROS induce and accelerate major skin aging cascades that result in decreased collagen production, increased expression of pro-inflammatory cytokines, and activation of MMPs.[24] The production of ROS initiates a cascade of events following the activation of mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF-κB) signaling pathways, which eventually leads to an increased expression of pro-inflammatory cytokines and MMPs and a decrease in the transforming growth factor-beta (TGF-β)/Smad signaling pathway and collagen synthesis (Fig. 3).[17]

3. Mechanism of action of polydeoxyribonucleotide

3.1. Activation of the A_{2A} receptor

The mechanism of action of PDRN involves the activation of the adenosine A_{2A} receptor.[25] Adenosine receptors have been recognized as promising targets for the management of ROS-related disorders. In particular, A_{2A} receptor activation can modulate the inflammatory response and apoptotic process and improve tissue repair and healing. The activation of A_{2A} receptors inhibits the NF-κB and MAPK signaling pathways, which are activated by ROS.[26] Blocking the NF-κB pathway inhibits the release of several pro-inflammatory cytokines and stimulates the release of anti-inflammatory cytokines.[27] Moreover, activation of the A_{2A} receptor increases cAMP concentration, which consequently inhibits the MAPK pathway.[26] PDRN inhibits MMP-1 expression and increases collagen synthesis.[28] Inhibition of the NF-κB and MAPK pathways clearly blocks the series of events initiated by ROS (Fig. 3).

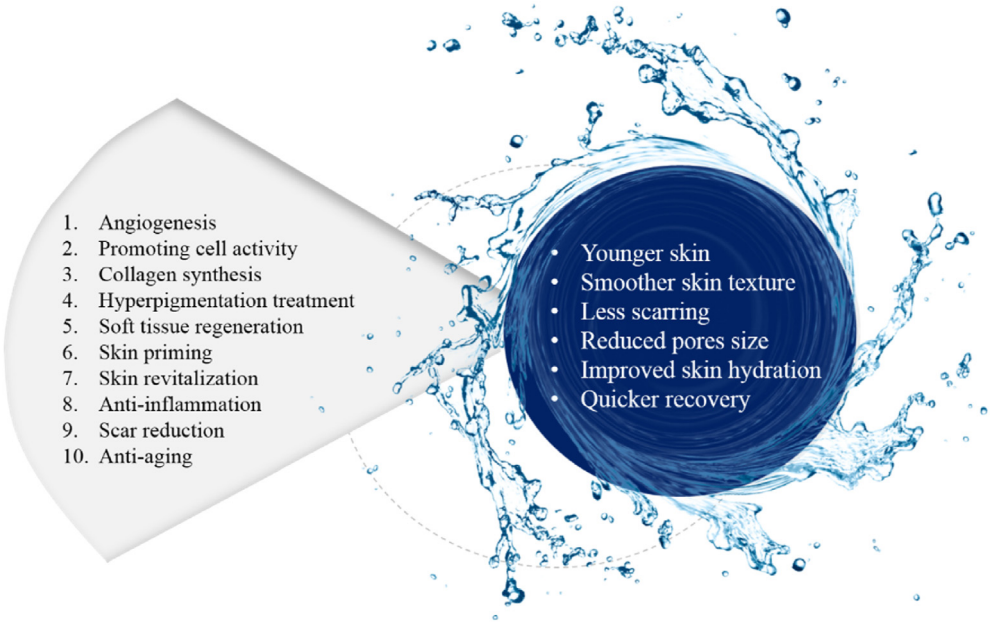

Fig. 2. Cosmetic effects of PDRN. PDRN, Polydeoxyribonucleotide.

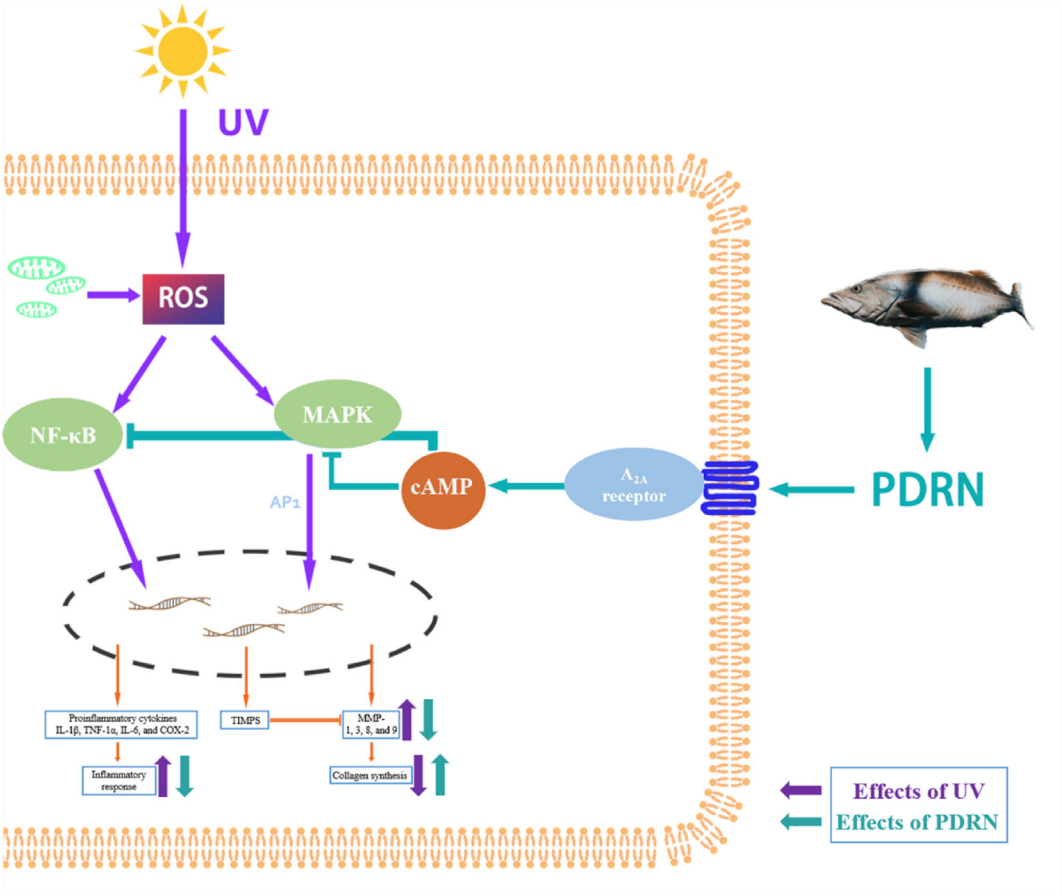

Fig. 3. Skin aging process and PDRN mechanism of action. The production of ROS initiates a cascade of events starting with the activation of the MAPK and NF-κB signaling pathways, which eventually lead to an increased expression of pro-inflammatory cytokines and MMPs and a decrease in TGF-β/Smad signaling and collagen synthesis. The mechanism of action of PDRN involves the activation of the A_{2A} receptor. This leads to the blocking of the NF-κB pathway, thus inhibiting the release of several pro-inflammatory cytokines and stimulating the release of anti-inflammatory cytokines. PDRN, polydeoxyribonucleotide; ROS, reactive oxygen species; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappa B; MMP, matrix metalloproteinase; TGF-β, transforming growth factor-beta; UV, ultraviolet; ROS, reactive oxidative species; cAMP, cyclic adenosine monophosphate; IL, interleukin; TIMPS, tissue inhibitors of metalloproteinases.

3.2. Collagen synthesis

Polynucleotides stimulate the binding of adenosine to the A_{2A} receptors, consequently promoting collagen synthesis. Western blotting analysis of human dermal fibroblasts (HDF) revealed that the application of polynucleotides resulted in a higher expression rate. A dose-dependent increase in collagen synthesis was also observed, which was absent in the cells treated with hyaluronic acid (HA).[14] In another study, the effect of the adenosine A_{2A} receptor agonist CGS-21680 on collagen synthesis was investigated. A significant dose-dependent increase in collagen synthesis was observed when cells were treated with the agonist.[29] Moreover, Fli1 was found to be a key player in the regulation of skin collagen homeostasis by repressing collagen genes. The activation of adenosine A_{2A} receptor in HDF with agonist CGS-21680 reduced Fli1 mRNA in the nucleus and promoted an increase in connective tissue growth factor (CTGF) mRNA and protein expression and secretion. These results are consistent with previous findings that Fli1 can directly inhibit CTGF expression, and that downregulation of Fli1 significantly upregulates CTGF. It was also noted that A_{2A} receptor activation resulted in an increase in collagen production, which was prevented by the neutralization of CTGF. These findings strongly suggest that the downregulation of Fli1 and upregulation of CTGF precede collagen induction upon A_{2A} activation.[30] Therefore, the stimulation resulting from adenosine binding to A_{2A} receptors initiates a cascade of events that eventually results in the synthesis of collagen.

3.3. Anti-inflammatory effect

PDRN induced an anti-inflammatory response in the murine macrophage cell line RAW 264.7, stimulated with a combination of zoledronic acid and lipopolysaccharides, and in the human chondrosarcoma cell line, stimulated with interleukin 1 beta (IL-1β). This suggests that PDRN possesses anti-inflammatory properties which manifest through the inhibition of inflammatory cytokines. This process is mediated by the activation of adenosine A_{2A} receptors, which regulate the cytokine network.[31,32] In another study, PDRN promoted the production of interleukin 10 (IL-10), an anti-inflammatory cytokine, and suppressed the production of nitric oxide and release of pro-inflammatory cytokines, interleukin 12 (IL-12), and tumor necrosis factor alpha (TNF-α).[33] In a study on the effect of PDRN on arthritis, increased IL-10 expression was observed.[34] Furthermore, a study conducted on a model of ischemic colitis using SD rats also demonstrated the anti-inflammatory activity of PDRN. Following treatment with PDRN, there was a reduction in the expression of inflammatory proteins, namely COX-2, IL-7, IL-1β, and TNF-α, as well as in the expression ratio of Bax/Bcl-2.[35] Another study that assessed the anti-inflammatory properties of PDRN in SD rats with LPS-induced lung injury also demonstrated suppression of IL-6 and TNF-α expression and a decrease in the expression ratio of Bax/Bcl-2. These findings support the promising anti-inflammatory properties of PDRN.[36]

3.4. Improved angiogenesis

PDRN has near-miraculous tissue-repair properties. It can improve the skin repair process by markedly increasing the expression of the vascular endothelial growth factor (VEGF), a master regulator of angiogenesis. PDRN stimulates VEGF production by activating the adenosine A_{2A} receptor. The resulting increase in CD31, transglutaminase-II, and angioprotein levels is suggestive of angiogenesis improvement. The healing effect of PDRN was found to be nullified by dimethyl-1-propargylxanthine (DMPX), a selective adenosine A_{2A} receptor antagonist, confirming the involvement of the adenosine A_{2A} receptor.[37]

The ability of PDRN to promote angiogenesis was also demonstrated in an experimental model of peripheral artery occlusive disease induced by femoral artery excision.[38] PDRN therapy increased VEGF expression and boosted robust blood flow restoration. Thermal injury is often characterized by poor skin repair and impaired angiogenesis. A study investigating the effects of PDRN therapy in mice following a burn injury showed enhanced burn wound re-epithelialization and a quicker recovery. The introduction of DMPX nullified the beneficial effects of PDRN therapy.[38] In another study using an experimental ischemic skin flap model, treatment with PDRN resulted in increased blood flow and VEGF expression.[39] These findings suggest that PDRN possesses angiogenic properties.

3.5. Inhibition of melanogenesis

PDRN significantly inhibits melanin synthesis in a dose-dependent manner. In addition, a significant reduction in intracellular tyrosinase activity was found in Mel-Ab cells following PDRN treatment, along with a decrease in melanocyte inducing transcription factor (MITF) and tyrosinase-related protein 1 (TRP-1). In another study, PDRN was shown to directly inhibit tyrosinase activity, thus significantly decreasing cellular melanin content in B16–F10 melanocytes. Similarly, a reduction in the protein expression of MITF, TRP-1, and TRP-2 was observed after treatment with PDRN. An enzymatic cascade strictly regulated by tyrosinase TRP-1 and TRP-2 results in the production of melanin from melanocytes.[40] Tyrosinase, responsible for the conversion of tyrosine to dopaquinone, is the main enzyme involved in the rate-limiting step of tyrosine metabolism, whereas MITF is an essential regulator of melanocyte survival, development, and proliferation and is also responsible for promoting the transcription of genes related to melanogenesis, such as tyrosinase and TRP-1.[38] In another study, the inhibitory effect of PDRN on melanogenesis was determined in Mel-Ab cells and a human melanocyte-keratinocyte co-culture, with findings similar to those of previous studies.[41] In conclusion, the suppression of melanogenesis occurs through the inhibition of melanogenic gene expression and tyrosinase enzymatic activity.[28]

4. Polydeoxyribonucleotide and its skin anti-aging effects

4.1. Improved skin texture

As aging progresses, collagen, the most abundant protein, undergoes organizational and structural changes, and undesired skin wrinkles become evident.[42] Collagen is one of the most abundant proteins in the human body and provides structural scaffolding for cells, tissues, and organs. It is a key player that determines skin physiology and provides strength and stability to tissues by creating support nets along the cellular structures.[43] There are many solutions available in the market to improve skin conditions, such as lasers, skin peelings, galvanic electricity, and oral supplements containing hydrolysate molecules. All of these procedures have a common goal, which is to enhance collagen production. Treatment with PDRN does improve collagen synthesis. A recent study investigated the increase in fibroblast collagen and elastin synthesis via the inhibition of MMP-1; the decrease in MMP activity resulted in an increase in collagen synthesis.[44] MMPs play an important role in elastin degradation,[45] and an increase in MMPs is associated with damage to ECM components. As mentioned above, PDRN inhibits the expression of MMP-1 and elastase. These two factors play a key role in skin aging and wrinkling. Elastase is a protease responsible for the breakdown of elastic fibers. The overexpression of elastase results in a loss of skin elasticity. An increase in elastase activity with age was found in the skin of mice. Therefore, elastase inhibition can slow down the process through which aging skin loses its elasticity.[46] MMP-1 is also involved in the breakdown of the ECM, thus the inhibition of MMP-1 via PDRN can also favor the maintenance of skin elasticity.

4.2. DNA synthesis

One of the key factors contributing to skin aging is the accumulation of DNA damage. Hence, DNA synthesis is essential for maintaining skin homeostasis. UV light plays a significant role in DNA damage. A study showed that UV-induced DNA damage initiates the release of MMP-1. Exposure to sunlight can trigger an increase in MMP-1 expression.[47] As mentioned above, PDRN can inhibit MMP-1. Furthermore, PDRN has the advantage of promoting angiogenesis and tissue regeneration. Blood vessels are the highways transporting oxygen and nutrients to the cells, but vascular growth requires VEGF. Polynucleotides stimulate VEGF production by activating the adenosine A_{2A} receptor to promote angiogenesis. Damaged and/or hypoxic tissue often cannot undergo *de novo* DNA synthesis. The nucleotides derived from PDRN provide purines and pyrimidine rings for the "salvage pathways." Salvage pathways help recover bases and nucleosides generated from DNA and RNA degradation, convert them back to nucleotides, and finally reincorporate them into DNA. PDRN contributes to DNA formation by generating nucleotides and nucleosides; this reactivates normal cell proliferation and growth patterns, leading to a faster tissue regeneration and wound healing.[6]

4.3. Treatment of hyperpigmentation

Melanin is key in determining the skin color of a person, and its overproduction and accumulation following extended exposure to UV irradiation or chronic inflammation can result in various hyperpigmentation skin disorders, such as melasma, mottled hyperpigmentation, freckles, senile lentigines, and post-inflammatory hyperpigmentation.[41] PDRN significantly inhibits melanin synthesis by suppressing melanogenesis via the inhibition of melanogenic gene expression and tyrosinase enzymatic activity.[28] This suggests that PDRN is a hypopigmentation agent that plays an important role in skin whitening. PDRN suppresses MITF and its target genes during melanogenesis. Furthermore, PDRN directly inhibits tyrosinase activity, the rate-limiting enzyme of melanogenesis.[28] The exact mechanism through which PDRN regulates tyrosinase inhibition is still not fully understood and should be investigated in the future. Although the skin-whitening effect of PDRN has been established, further research in this field is required.

4.4. Hair regeneration

Pattern hair loss (PHL) is defined as the non-scarring progressive thinning of hair characterized by a gradual decrease in the number of hairs, especially in the frontal, central, and parietal scalp, due to a process known as follicular miniaturization.[48] This common form of alopecia affects millions of people worldwide and can be cosmetically disrupting. Previous studies have stated that 1 927-nm fractionated thulium laser energy is a safe approach for PHL treatment.[49] Two studies combined this treatment with PDRN to improve results.[50,51] In the first study, patients were divided into two groups: one group received fractionated thulium laser and PDRN injection, while the other group received PDRN injection only. None of the patients were on topical or oral hair loss medication. The results indicated that the combined therapy greatly improved the mean hair thickness and hair count compared to PDRN injection alone.[50] The second study presented the case of a patient who showed

improvements in hair thickness and hair count after a combined therapy of 1 927-nm fractionated thulium laser and PDRN injections.[51] These studies suggest the addition of PDRN injections improved the benefits of thulium laser therapy in the treatment of hair loss. Another study was conducted to investigate the effects of PDRN injection combined with platelet-rich plasma (PRP) therapy on hair regeneration. Patients were divided into two groups: one group received PRP and PDRN combined therapy, while the other group received PDRN therapy alone. The results concluded that both groups exhibited improvements in mean hair thickness and hair count. The comparison analysis between the two groups suggested that the combined therapy improved hair thickness but not hair count as compared to PDRN therapy.[52] Nevertheless, these findings suggest improved hair health following PDRN treatment.

5. Mode of use

Dermal fibroblasts are the major component of the skin; they not only serve as the building blocks of collagen, but also play a crucial role in the regulation of skin physiology.[53] Polynucleotides promote the growth and activity of fibroblasts.[54,55] Fibroblasts are located in the dermal layer, suggesting that polynucleotides must be administered directly into this layer to obtain maximum benefits. This can be achieved, for example, through direct penetration or the use of a fractional CO_2 laser. The laser creates micro-channels that reach the dermal layer, allowing polynucleotide-containing products to directly reach the dermis when applied to the skin. Similarly, microneedling can be used to increase the absorption of PDRN by creating tiny holes in the skin. Mesotherapy (also known as biorevitalization) consists in the restoration or supplementation of the loss in skin nourishment. Skin boosters help and encourage the skin to increase its functions. These are biological or bioactive compounds that originally involved the use of HA, but, over time, evolved to include a spectrum of substances.[56] The dermal ECM naturally contains HA, which plays a key role in the maintenance of skin elasticity, hydration, and firmness. As aging progresses, a significant reduction in the amount of glycosaminoglycans leads to a reduction in skin elasticity, hydration, and overall quality.[57] Thus, the use of HA fillers plays an important role in improving skin elasticity and hydration and compensating for volume loss.

Although HA seems vital for skin revitalization, the introduction of polynucleotides paves the way for novel skincare solutions owing to their extraordinary properties, thus expanding the scope of "biorevitalization". PDRN has significant properties with regards to tissue repair, anti-inflammation, hyperpigmentation reduction, increase of collagen synthesis, and overall improvement of skin texture.[9,14,16,28,58]

6. Safety of use

PDRN is extracted and purified at very high temperatures. This procedure allows for the recovery of more than 95% pure active substances with inactivated proteins and peptides. Therefore, the safety of the product is guaranteed because of the absence of any immunological effect.[6] A study in mice and rats was conducted to evaluate the toxic effects of repeated systemic administration of PDRN. Macroscopic and microscopic analyses found no toxicity in brain, heart, skeletal muscle, liver, or lung samples. Overall, excellent tolerability was observed.[59] In another study, the effects of PDRN on the healing of chronic diabetic foot ulcers were investigated, and the safety of the treatment was evaluated. Safety and tolerability were excellent, indicating that treatment with PDRN was effective and safe.[60] Furthermore, the evaluation of safety after treatment with polynucleotide fillers exhibited no side effects and seemed to be a safe treatment for skin rejuvenation.[61] In another study, the safety of a composite filler consisting of HA and polynucleotides was evaluated *in vitro* and *in vivo*. The composite fillers exhibited excellent biocompatibility and biodegradability. The *in vitro* results also showed that the composite fillers were completely degraded *in vivo* within a specific period. These findings provide compelling evidence for the safety of the product.[14]

Although very few clinical studies have been conducted on the safety of polynucleotides, most have shown promising results. A study of 40 patients was conducted to evaluate the safety and effectiveness of PDRN injections. During the study period, the participants reported no severe adverse effects and no persistent skin abnormalities were observed on physical examination. No serious systemic adverse events occurred in any subject, according to vital signs or laboratory data. A significant improvement was observed, and no injection-related complications were reported.[62] Another study was conducted to investigate the effect of PDRN on diabetic foot ulcers. All patients exhibited good signs of improvement with no related complications.[60] Another clinical study reported an improvement in tissue oxygenation, inflammation, and angiogenesis following PDRN treatment.[12] A clinical study also demonstrated the positive effects of PDRN on skin grafts, without any adverse effects.[63]

7. Discussion

Aging is an inevitable process that begins from the moment we are born. The skin, being the largest human organ, serves as a barrier between the organs and the outside world. The underlying changes in the structure of the skin directly correspond to visible signs of aging. Aging skin is characterized by the disappearance of dermal papillae, skin atrophy, and disruption of the dermal ECM. There is an obvious decline in the surface area of the dermal-epidermal interface, which contributes to increased skin fragility and reduced nutrient transfer between the dermis and the epidermis.[64] Collagen is the major component of the dermal-epidermal interface. Therefore, collagen synthesis can slow down the degradation of this structure. Additionally, there is a rapid increase in MMPs. Unlike other organs, the skin is not only affected by intrinsic factors but also by extrinsic factors. Although the mechanism of skin aging is not fully understood, ROS accumulation can lead to lipid, protein, nucleic acid, and organelle damage. ROS initiate a cascade of events following the activation of the MAPK and NF-κB signaling pathways, which eventually forms the core mechanism of skin aging. PDRN, a potential anti-aging agent, has numerous effects that are opposite those of skin aging. Although PDRN has numerous therapeutic properties, further research is required to identify more cost-effective extraction methods and maximize its use in the cosmetic industry. PDRN is a hypopigmentation agent; inhibition of tyrosinase and downregulation of MITF result in a reduction of melanogenesis.[28] Although the use of PDRN as a skin-whitening agent has been established, further animal studies and clinical trials are required. One of the most apparent properties of the skin is its function as a physicochemical barrier. The largest human organ can resist the penetration of many molecules, but smaller particles can penetrate through the corneal layer. The 500 Da rule establishes that for a molecule to be able to cross the skin barrier, it must have a molecular weight lower than 500 Da.[65] This raises a concern on whether polynucleotide-containing cosmetics can in fact have a beneficial effect on skin quality. Although the term mesotherapy basically refers to the biorevitalization of the skin, there is a difference in the concept, ingredients, and mechanism of action of both PDRN therapy and skin boosting with HA. The benefits of each can be understood based on the ingredients used. The main goal of polynucleotide therapy is anti-aging, whereas skin boosters with HA mainly focus on deep hydration of the skin. The benefits of PDRN therapy include reversal of the signs of aging with reduction of fine lines and wrinkles, a more elastic and firm skin texture owing to enhanced collagen formation, repair of damage caused by chronic inflammation or prolonged sunlight exposure, scar reduction, improved skin hydration and barrier function, and an overall improvement in skin quality.

Conversely, the benefits of HA therapy include soft tissue augmentation, which gives fullness to the sunken/depressed areas, deep hydration of the skin, and improvement of wrinkles, fine lines, and pore size with the addition of the botulinum toxin. In addition, skin whitening can

be achieved with the addition of vitamin C. Although the main purpose of both therapies is to achieve an overall anti-aging effect, the mechanism of action is different. While HA provides a beneficial effect through soft tissue augmentation, PDRN therapy focuses on tissue regeneration. Mesotherapy currently involves the use of HA as the main player in skin revitalization. The introduction of polydeoxyribonucleotides, however, leads to novel concepts and solutions for skin rejuvenation, thereby expanding the scope of mesotherapy.

8. Conclusion

Based on its well-known mechanism of action, PDRN can potentially improve skin quality, slow down aging, and improve dermal regeneration. However, further research will help reveal the multidimensionality and benefits of PDRN use.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All the authors have consented for the publication.

Authors' contributions

Khan A: Methodology, Investigation, Writing-Original draft. Wang G: Methodology, Investigation, Writing-Original draft. Zhou F: Methodology, Investigation, Writing-Original draft. Cui H: Conceptualization, Supervision. Gong L: Writing-Review and editing. Zhang J: Writing-Review and editing. Qi L: Writing-Review and editing.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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