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# Therapeutic Potential of *Polydeoxyribonucleotide (PDRN)* in Dermatology and Aesthetic Medicine: Molecular Mechanisms and Anti-Aging Applications

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## Abstract

*Polydeoxyribonucleotide (PDRN)*, a biopolymer derived from DNA, predominantly sourced from salmon sperm, has garnered attention as a potential therapeutic agent in the realms of dermatology and aesthetic medicine. This interest is largely attributed to its regenerative, anti-inflammatory, and antioxidant characteristics. The mechanism of action of PDRN primarily involves the selective activation of adenosine A2A receptors, alongside complementary salvage pathways. Through these processes, PDRN facilitates collagen synthesis, promotes fibroblast proliferation, encourages angiogenesis, aids in DNA repair, and modulates inflammatory mediators. The body of evidence from both preclinical and clinical investigations underscores the efficacy of PDRN in enhancing skin elasticity, diminishing wrinkles, improving wound healing, reducing acne scars, stimulating hair growth, and alleviating hyperpigmentation. Moreover, its commendable safety profile and biocompatibility further bolster its potential for clinical application. This literature review aims to consolidate the existing knowledge surrounding the molecular mechanisms and therapeutic uses of PDRN within the context of anti-aging dermatology. However, despite the encouraging results, there remains a pressing need for additional research to establish standardized treatment protocols, ascertain optimal dosages, and assess long-term outcomes. In summary, PDRN stands as an innovative and adaptable asset in the fields of regenerative and aesthetic medicine, effectively bridging the gap between molecular biology and clinical practice in the quest for skin rejuvenation.

**Keywords:** *Polydeoxyribonucleotide*; Skin Aging; Regenerative Medicine; Dermatology; Aesthetic Therapy

**Abbreviations:** PDRN**:** *Polydeoxyribonucleotide*; PNs: *polynucleotides*; UV: Ultraviolet Radiation; ROS: Reactive Oxygen Species; MMPs: matrix metalloproteinases; SASP: Senescence-Associated Secretory Phenotype; VEGF: Vascular Endothelial Growth Factor; ECs: Endothelial Cells; iNOS: Inducible Nitric Oxide Synthase; FPHL: Female Pattern Hair Loss; PRP: Platelet-Rich Plasma

## Introduction

The process of skin aging is an unavoidable phenomenon, shaped by both intrinsic elements, including genetic predispositions and hormonal fluctuations, as well as extrinsic influences, such as exposure to ultraviolet radiation, environmental pollutants, and various lifestyle choices [1-3]. These factors contribute to the deterioration of skin integrity, leading to visible signs such as wrinkles, sagging, and a loss of moisture [1,4]. In contemporary practice, there is a marked preference for minimally invasive interventions- such as injectables, dermal fillers, chemical peels, and laser treatments- over more traditional surgical options [2,5,6]. This shift reflects a growing recognition of the need for effective yet less invasive solutions to address the challenges posed by skin aging.

The field of regenerative and aesthetic medicine has increasingly focused on the significance of *polynucleotides* (PNs), which are recognized for their capacity to modulate gene expression and facilitate tissue repair [7,8]. These compounds, which consist of nucleotides- the fundamental components of DNA and RNA- are integral to various essential cellular functions, such as proliferation, differentiation, and survival [8,9]. In the realm of aesthetic treatments, the efficacy of PNs has been evidenced through their ability to enhance skin texture, improve elasticity,

diminish the depth of wrinkles, promote hair growth, and refine the appearance of scars [10-12].

In the realm of dermatology and regenerative medicine, *polydeoxyribonucleotide (PDRN)*, a type of PN sourced from salmon sperm, has surfaced as an exceptionally promising biomaterial [13,14]. This compound consists of a blend of deoxyribonucleotides, which play a pivotal role in promoting cell proliferation, facilitating angiogenesis, and enhancing tissue repair, all while demonstrating notable anti-inflammatory properties. The diverse effects of PDRN are primarily driven by the activation of adenosine A2A receptors alongside other significant intracellular pathways [15-20].

This literature review aims to compile recent scientific findings concerning the biological mechanisms, clinical applications, and therapeutic effects of certain interventions across multiple areas. These areas include skin rejuvenation, wound healing, hair growth, modulation of pigmentation, and strategies for combating aging. Such an exploration underscores their potential as groundbreaking tools within the realms of regenerative and aesthetic medicine.

## Methodology

This investigation constitutes a literature review that delves into the therapeutic roles of *polydeoxyribonucleotide (PDRN)* within the realms of dermatology and anti-aging medicine. The process of data acquisition involved meticulously structured searches across various international scientific databases, such as PubMed, Scopus, ScienceDirect, and Web of Science. These searches utilized a combination of keywords, including "*polydeoxyribonucleotide*," "*polynucleotides*," "skin aging," "dermatology," "aesthetic medicine," and "regenerative medicine." The criteria for inclusion were stringent, encompassing peer-reviewed original articles, systematic reviews, and clinical trials that were composed in English. These works specifically focused on the chemical composition, biological mechanisms, and clinical applications of PDRN in areas such as skin rejuvenation, wound healing, pigmentation disorders, hair growth stimulation, and anti-aging treatments. Conversely, studies that did not pertain to dermatological or aesthetic applications, duplicates, and publications that lacked methodological rigor or comprehensive information were systematically excluded from consideration. The results were systematically categorized thematically, thereby reinforcing the underlying theoretical framework.

## Theoretical Framework

### Anti-Aging Effects

Aging represents an inherent and irreversible biological phenomenon that is natural to all humans, yet it manifests in a non-uniform manner across individuals [21]. This chronic physiological process begins at birth and persists until the end of life, leading to gradual alterations in cellular and tissue functions [21,22]. The decline in functionality is observable across various organ systems, with the skin being particularly vulnerable and visibly impacted [23]. The aging of the skin is marked by both structural and functional changes that adversely affect its aesthetic appeal and physiological capabilities [22,24]. Notably, a significant reduction in collagen production and the gradual deterioration of elastic fibers are prominent alterations, resulting in diminished tissue support and muscle tone [22]. Concurrently, there is a decline in levels of hyaluronic acid, a crucial molecule for sustaining skin hydration [25]. These transformations lead to a thinning of the epidermis, the emergence of wrinkles, and instances of hyperpigmentation, ultimately rendering the skin less vibrant and dull in appearance [26].

In addition to the aesthetic consequences, the aging process of the skin carries functional implications. The hydrolipidic barrier's efficiency diminishes, which increases susceptibility to xerosis and enhances *transepidermal* water loss [23]. Moreover, there is a reduction in fibroblast activity and vascular support, which contributes to a deceleration in tissue repair and wound healing processes [24]. These alterations, coupled with visible changes that directly influence self-perception, fuel the rising demand for aesthetic and dermatological treatments aimed at mitigating the signs of aging [21].

### Mechanisms of Skin Aging

#### Intrinsic and Extrinsic Aging

Aging of the skin, a natural and unavoidable physiological phenomenon, is a process that every individual encounters throughout their lifetime. This phenomenon can traditionally be categorized into two primary types: intrinsic aging and extrinsic aging [27]. While intrinsic aging is associated with genetic predispositions and the passage of time, extrinsic aging is largely influenced by environmental factors and lifestyle choices [26,27]. Despite their differing origins, both intrinsic and extrinsic aging lead to significant structural and functional changes in the skin, ultimately impacting its quality, texture, and overall aesthetic appeal [27]. Thus, understanding the distinction between these two forms of aging is crucial for comprehending how internal and external factors interact in the gradual deterioration of skin health [28].

Intrinsic aging, often referred to as chronological aging, occurs regardless of external environmental influences and is intricately linked to genetic factors, hormonal influences, and the metabolism of cells [27]. The clinical signs of this type of aging manifest as fine lines, dryness of the skin, thinning of the epidermis, and a gradual decline in elasticity [29,30]. These indicators are reflective of diminished cellular activity, a reduction in the proliferation of keratinocytes and fibroblasts, and a progressive atrophy of the dermis [28,29]. A pivotal aspect of this process is cellular senescence, which is characterized by a reduced capacity for basal cells to proliferate and a depletion of collagen and elastic fibers,


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ultimately undermining the structural integrity of the skin [28].

Extrinsic aging, commonly referred to as photoaging, is primarily the result of prolonged exposure to various external elements. These include ultraviolet (UV) radiation, environmental pollutants, tobacco use, psychological stressors, and suboptimal lifestyle choices [27]. Clinically, this form of aging manifests through pronounced deep wrinkles, changes in pigmentation, solar elastosis, and a significant decline in skin elasticity [31]. Among these external factors, ultraviolet radiation stands out as the most detrimental, accounting for nearly 80% of the aging observed in facial skin. This is due to its capacity to provoke oxidative stress, trigger cellular apoptosis, enhance melanogenesis, and lead to the breakdown of structural proteins within the extracellular matrix [28].

**Role of Reactive Oxygen Species**

The intricate interplay of reactive oxygen species (ROS) is pivotal in the processes of skin aging, both intrinsic and extrinsic [32]. Among the various ROS, notable entities include superoxide anion, hydrogen peroxide, hydroxyl radical, singlet oxygen, lipid peroxides, and nitrogen oxides. These molecules are characterized by their high reactivity, enabling them to engage with crucial biomolecules, including proteins, lipids, and nucleic acids [33]. While ROS fulfill essential regulatory roles at physiological concentrations- contributing to inflammatory responses and cellular signaling- excessive production leads to oxidative stress, which undermines the structural and functional integrity of skin cells [32].

The generation of ROS within the skin is a continuous process, predominantly driven by aerobic mitochondrial respiration, which accounts for approximately 1.5 to 5% of cellular oxygen consumption [33,34]. Furthermore, enzymes such as NADPH oxidases play a significant role in the regulated production of ROS, which, when maintained at appropriate levels, are essential for various physiological functions, including immune defense and hormone synthesis [35]. However, an imbalance between the production and neutralization of ROS can precipitate oxidative stress, leading to detrimental outcomes such as DNA mutations, oxidation of proteins and lipids, and disruptions in cellular signaling pathways- factors that collectively hasten the aging of the skin [36].

At the molecular level, the activation of multiple signaling pathways by ROS is crucial for the remodeling of the extracellular matrix [36]. Key consequences of this activation include diminished collagen synthesis, the stimulation of matrix metalloproteinases (MMPs) that degrade connective tissue proteins, and the induction of the senescence-associated secretory phenotype (SASP). The SASP is particularly noteworthy as it fosters chronic inflammation, further accelerating the deterioration of the skin [37]. Thus, the role of ROS in skin aging is paradoxical: while they serve as vital signaling molecules at physiological levels, their excess transforms them into harmful agents that jeopardize cellular integrity, manifesting in clinical signs such as wrinkles, sagging, and diminished skin radiance [35].

## Polydeoxyribonucleotide (PDRN): Structure, Chemistry, and Mechanisms of Action

In recent years, *polydeoxyribonucleotide (PDRN)*, a biopolymer primarily sourced from the DNA of salmon sperm (specifically from species such as *Oncorhynchus keta* and *Oncorhynchus mykiss*), has garnered significant interest within the realm of regenerative medicine. This growing attention can be attributed to its diverse therapeutic properties [38]. PDRN is characterized by its linear structure, which consists of deoxyribonucleotide units that correspond to both *purine and pyrimidine nucleotides*. Notably, it adopts a double-helix conformation, a feature that not only contributes to its structural integrity but also enhances its biological functionality [19,39]. The molecular weight of PDRN varies considerably, ranging from 50 to 1500 kDa, with the majority of its fragments falling between 80 and 200 kDa. This variation underscores the molecular heterogeneity inherent in PDRN [19]. To ensure clinical safety, PDRN is subjected to stringent extraction and purification processes, achieving a high purity level of over 95%. These meticulous procedures are crucial as they minimize the risk of adverse immunological reactions by effectively removing proteins, peptides, and lipids from the final product [10].

The biological functionality of PDRN is intricately associated with its chemical composition. The DNA chains, which are interconnected through phosphodiester bonds, exhibit a remarkable resistance to enzymatic degradation. This characteristic not only enhances the durability of PDRN but also significantly boosts its pharmacological efficacy [39]. Each nucleotide unit is composed of a pentose sugar, a phosphate group, and a nitrogenous base- either a *purine or a pyrimidine*. These components are linked by a $\beta$-N-glycosidic bond, facilitating specific interactions with cellular repair mechanisms [10]. Furthermore, the source of DNA derived from sperm contributes to the molecule's exceptional purity, ensuring the absence of residual cellular components typically found in somatic tissues [10,38].

The regenerative properties of PDRN are primarily mediated through the selective stimulation of the adenosine A2A receptor, which is a G protein-coupled receptor that plays a crucial role in various processes, including neuromodulation, vascular function, and immune responses [14,36]. Upon binding to this receptor, a series of intracellular signaling cascades are triggered, leading to the inhibition of the NF-κB and MAPK pathways. This inhibition results in a decrease in inflammatory responses while simultaneously fostering anti-inflammatory effects [36-39]. In addition to these effects, the activation of the A2A receptor also promotes collagen production in fibroblasts. This occurs through the downregulation of MMP-1, which is essential for


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tissue regeneration and the healing of wounds [14]. In addition to this, there exists a complementary mechanism known as the salvage pathway. In this process, nucleotides and nucleosides that are released during the degradation of PDRN are repurposed for DNA synthesis. This promotes cellular restoration and tissue proliferation while maintaining a balanced energy demand [10,40].

## Polynucleotides for General Skin Conditions

*Polynucleotides* (PNs), with a particular emphasis on PDRN, have surfaced as noteworthy therapeutic agents in addressing skin modifications, primarily due to their mechanisms aimed at tissue regeneration and the fortification of the dermal matrix [17]. A pivotal molecular mechanism involves the activation of adenosine A2A receptors located in dermal fibroblasts- these cells play a crucial role in collagen production and the preservation of extracellular matrix integrity [39]. Moreover, beyond merely stimulating collagen production, PNs facilitate the proliferation and functional activation of fibroblasts, which in turn leads to enhanced dermal density and the restoration of skin physiology [41]. Therapeutic approaches that enhance the direct infiltration of PDRN into the dermis, such as microneedling and fractional $CO_2$ laser treatments, have been linked to the amplification of its regenerative properties [39]. Additionally, a significant mechanism worth noting is PDRN's capacity to induce angiogenesis, which is mediated by the upregulation of vascular endothelial growth factor (VEGF) expression through the A2A receptor. This process ensures an augmented supply of oxygen and nutrients to the tissues, thereby facilitating repair and healing processes [39-41].

The multifaceted applications of PNs in addressing various skin conditions reveal a broad array of clinical uses, each supported by differing degrees of evidence. Notably, research has explored their function as skin boosters, which are designed to enhance skin texture, elasticity, and hydration [42,43]. Furthermore, PNs are being investigated for their potential as cutting-edge delivery systems for cosmeceuticals, which may improve the bioavailability and stability of active ingredients [44]. In addition to these roles, recent studies have documented the advantages of PNs in rejuvenating neck skin [45] and their effectiveness in combined bio revitalization protocols [46]. Moreover, expert reviews and case series have underscored the application of PNs in topical approaches to combat skin aging [47]. This is particularly relevant in the context of emerging trends within anti-aging dermatology [48], where PNs are being recognized as promising alternatives to traditional facial fillers [49].

## Effects on Wound Healing

The intricate phenomenon of wound healing unfolds through a tripartite sequence: inflammatory, proliferative, and remodeling stages. Initially, the focus is on achieving hemostasis, which encompasses the mobilization of leukocytes and monocytes, alongside various vascular and cellular reactions [50]. Following this, white blood cells secrete growth factors that catalyze the onset of the proliferative phase. During this critical period, fibroblasts and endothelial cells (ECs) play a pivotal role in synthesizing collagen and ground substance, thereby reinstating the integrity of the tissue. Furthermore, angiogenesis is vital, as it guarantees an adequate supply of nutrients essential for the formation of new tissue [51,52]. The therapeutic application of PDRN has garnered attention as a significant approach in managing intricate wounds, such as severe burns and chronic ulcers that present challenges in healing [53].

Wound healing represents a complex and dynamic phenomenon characterized by several interrelated phases, including hemostasis, inflammation, proliferation, maturation, and remodeling. This intricate process involves a variety of cellular participants, such as fibroblasts, keratinocytes, endothelial cells, and immune cells [38]. Notably, PDRN emerges as a significant factor in this context, as it promotes cellular migration and proliferation while also enhancing collagen expression. Collagen serves as a vital structural element necessary for the restoration of the extracellular matrix [54]. Moreover, PDRN exerts another important influence by modulating the inflammatory response. This modulation occurs through the inhibition of apoptosis and the downregulation of pro-inflammatory mediators, including inducible nitric oxide synthase (iNOS), IL-1$\beta$, IL-6, and TNF-$\alpha$. These mediators are well-documented contributors to the progression of tissue damage [38].

## Polynucleotides for Wrinkle Treatment

The significance of PNs as biomolecules in the realm of aesthetic medicine has become increasingly pronounced, particularly owing to their regenerative properties that positively influence skin health and their effectiveness in diminishing facial wrinkles. Clinical studies have substantiated that PNs promote collagen production, enhance skin elasticity, and improve dermal hydration, leading to notable advancements in skin texture and overall quality [55]. These beneficial outcomes can be attributed to the capacity of PNs to influence the cutaneous microenvironment. This is achieved through the secretion of growth factors that activate fibroblasts and keratinocytes, thereby stimulating the synthesis of collagen and hyaluronic acid- two critical components in the process of facial rejuvenation [56]. Among the various derivatives studied, PDRN is particularly noteworthy for its pivotal role in maintaining the extracellular matrix. It does so by inhibiting the activity of degradative enzymes, including MMP-1 and elastase, which are closely linked to the processes of skin aging and the formation of [14].

Moreover, randomized controlled trials have illustrated that fillers based on PNs yield outcomes that are either superior to or at least on par with those of conventional fillers, such as hyaluronic acid. These studies indicate notable enhancements in skin


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elasticity, texture, and the longevity of effects [55,57]. Additionally, other research has highlighted a more rapid onset of action and a reduced incidence of adverse reactions when compared to biostimulators like polycaprolactone [58]. Furthermore, these fillers have demonstrated commendable safety and tolerability in aesthetically sensitive regions, including the periocular and canthal lines [59]. Systematic reviews, along with expert consensus, further bolster the assertion that PNs are effective in stimulating collagen synthesis, mitigating inflammation, and fostering tissue regeneration. This positions them as promising candidates for bio revitalization and facial rejuvenation [59-62].

### Antimelanogenic Effects

Melanogenesis, a process predominantly orchestrated by melanocytes, is modulated by factors derived from keratinocytes. This intricate process relies heavily on specific enzymes, including tyrosinase, TRP-1, TRP-2, and the transcription factor MITF, which are essential for the synthesis of melanin [63-65]. In experimental settings, it has been demonstrated that PDRN significantly diminishes melanin production in cultures of melanocytes, and this reduction occurs in a dose-dependent manner [66]. The underlying mechanism involves the suppression of intracellular tyrosinase activity, alongside a downregulation of the expression levels of MITF, tyrosinase, and TRP-1 [17]. Additionally, PDRN's activation of adenosine A2A receptors initiates a cascade that results in the phosphorylation of ERK and AKT, further enhancing the inhibition of melanogenesis [66]. Moreover, PDRN's influence extends beyond the enzymatic pathways of melanogenesis; it also plays a role in modulating inflammatory processes that can exacerbate cutaneous hyperpigmentation. Collectively, these findings illuminate the complex interplay of molecular mechanisms through which PDRN operates, reinforcing its potential as a therapeutic agent in the management of hyperpigmentation.

### Anti-Hair Loss Effects

The exploration of PNs has surfaced as a noteworthy alternative in the realm of alopecia treatment, directly influencing the molecular mechanisms that govern the hair follicle cycle [67]. Female pattern hair loss (FPHL), a specific variant of androgenetic alopecia, is marked by a gradual process of follicular miniaturization, which results in the thinning of terminal hairs, especially noticeable in the frontal and vertex areas of the scalp [68,69]. In this context, PDRN has emerged as a promising therapeutic agent for managing FPHL. A clinical investigation revealed that intra-perifollicular injections of PDRN, whether administered alone or in conjunction with platelet-rich plasma (PRP), led to significant enhancements in hair count and thickness when compared to control groups. Notably, the combination therapy demonstrated even more pronounced improvements in hair thickness [70]. Moreover, beyond its influence on the Wnt/$\beta$-catenin signaling pathway, PNs also activate purinergic A2 receptors found in dermal papilla cells. This activation is crucial as it extends the anagen phase, mitigates hair loss, and promotes an increase in hair shaft thickness [11]. These observations underscore the potential of PDRN not only in fostering follicular regeneration but also as a valuable adjunctive treatment option for individuals experiencing alopecia.

## Conclusion

The therapeutic potential of PDRN has garnered significant attention in the realm of anti-aging dermatology, primarily attributed to its regenerative, anti-inflammatory, and antioxidant characteristics. This compound operates chiefly through the selective activation of adenosine A2A receptors, alongside engaging complementary salvage pathways. Such mechanisms facilitate essential processes in skin rejuvenation, including collagen synthesis, fibroblast proliferation, angiogenesis, and DNA repair. Clinical and experimental investigations underscore the efficacy of PDRN in enhancing skin elasticity, diminishing the appearance of wrinkles, promoting wound healing, alleviating acne scars, stimulating hair growth, and reducing hyperpigmentation. Notably, the safety profile of PDRN appears to be quite favorable, with clinical reports indicating no significant adverse effects associated with its use. Nevertheless, it is imperative to conduct further research to establish standardized treatment protocols, determine optimal dosages, assess long-term outcomes, and evaluate its comparative effectiveness relative to other established dermatological treatments.

## Authors' Contributions

Investigation, conceptualization, methodology, writing - original draft, S.J.S; Conceptualization, formal analysis, writing-reviewing and editing, supervision, validation, R.C.

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