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Polydeoxyribonucleotides derived from salmon: Potential aesthetic applications and mechanisms of action

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ABSTRACT: Polydeoxyribonucleotides (PDRNs) are naturally occurring polymers comprised of deoxyribonucleotides linked by phosphodiester bonds. PDRNs derived from various sources, including salmon, have gained significant attention in aesthetics due to their potential regenerative and anti-aging properties. Skin aging is a complex processinfluenced by various intrinsic and extrinsic factors. It involves the progressive loss of collagen, elastin, and hyaluronic acid, resulting in wrinkle formation, dryness, and reduced elasticity. Traditional approaches such as topical creams, laser therapy, and dermal fillers have provided some improvements, but there is a growing demand for more natural and effective alternatives.This review article aims to explore the utilization of salmon-derived PDRNs in aesthetic medicine, focusing on their mechanisms of action and specific applications in skin rejuvenation.

KEYWORDS: Polydeoxyribonucleotides, salmon, aestheticmedicine, PDRN, anti-aging

I. INTRODUCTION

Nucleic acid-based compounds, such as DNA (deoxyribonucleic acid) and RNA (ribonucleic acid), are increasingly being used in aesthetic medicine for various purposes.

These compounds have unique properties that make them useful in improving the appearance and health of the skin. Here is some background on their use in aesthetic medicine as SHIN, Jung Won et al.(2019) says:

a) Stimulating collagen production: Collagen is a protein responsible for maintaining the structure, elasticity, and firmness of the skin. With age, collagen production decreases, leading to the formation of wrinkles and sagging skin. Nucleic acid-based compounds can help stimulate collagen synthesis, promoting skin rejuvenation and reducing the signs of aging.

b) Enhancing wound healing: Nucleic acids play a crucial role in the wound healing process. They are involved in cell proliferation, tissue repair, and the formation of new blood vessels. By applying nucleic acid-based compounds to wounded or damaged skin, the healing process can be accelerated, resulting in faster tissue regeneration and reduced scarring.

c) Promoting skin hydration: Hydration is essential for maintaining healthy and youthful-looking skin. Nucleic acid-based compounds have the ability to improve the skin's ability to retain moisture, leading to increased skin hydration. This can result in a smoother, plumper, and more radiant complexion.

d) Repairing sun-damaged skin: Exposure to the sun's harmful ultraviolet (UV) rays can cause significant damage to the skin, including premature aging, pigmentation disorders, and even skin cancer. Nucleic acid-based compounds can help repair sun-damaged skin by promoting the removal of damaged cells and stimulating the production of healthy skin cells.

e) Treating hyperpigmentation: Hyperpigmentation refers to the darkening of specific areas of the skin caused by an overproduction of melanin (the pigment responsible for skin color). Nucleic acid-based compounds can help regulate melanin production and reduce the appearance of hyperpigmentation, resulting in a more even skin tone.

f) Enhancing the effectiveness of other treatments: Nucleic acid-based compounds can also be used in combination with other aesthetic treatments, such as laser therapy or dermal fillers, to enhance their effectiveness. They can improve the delivery and absorption of active ingredients, resulting in better treatment outcomes.

In accordance to Garner (2021), it's important to note that the use of nucleic acid-based compounds in aesthetic medicine is still evolving, and more research is being conducted to fully understand their potential benefits and limitations. Additionally, these compounds should only be used un-

der the supervision of trained medical professionals to ensure safety and efficacy.

II. SALMON-DERIVED POLYDEOXYRIBONUCLEOTIDES

PDRNs are a type of nucleic acid composed of deoxyribonucleotide monomers, which are the building blocks of DNA.

"Polydeoxyribonucleotides (PDRNs) are a family of DNA-derived drugs with a molecular weight ranging from 50 to 1500 kDa, which are mainly extracted from the sperm cells of salmon trout or chum salmon" (KIM, 2021) .

The composition of salmon-derived PDRNs includes four different types of deoxyribonucleotide monomers: adenine (A), cytosine (C), guanine (G), and thymine (T). These monomers are arranged in a specific sequence to form a single stranded chain of PDN.

The structure of salmon-derived PDRNs resembles a linear, single-stranded DNA molecule. Each deoxyribonucleotide monomer is connected to the next through phosphodiester bonds, forming a backbone of the PDRN chain. The sequence of the deoxyribonucleotide monomers determines the specific genetic information encoded by the PDRN.

PDRNs extracted from salmon generally have a relatively short length compared to the DNA found in the nucleus of cells. They typically consist of 10 to 50 nucleotides, although longer PDRNs with up to several hundred nucleotides can also be found.

The specific functional properties of salmon-derived PDRNs are still being studied, but they have been found to have various biological activities, such as immune modulation, anti-inflammatory effects, and promotion of cell regeneration. These properties make PDRNs potential candidates for therapeutic applications in medicine and skincare.

III. EXTRACTION AND PURIFICATION METHODS FOR OBTAINING PDRNS FROM SALMON

Extracting and purifying polydeoxyribonucleotides (PDRNs) from salmon sperm for aesthetic use typically involves more specialized processes to ensure high purity and sterility (European Patent Aplication, 2022). Here are some common methods used:

a) Sperm Collection: Salmon sperm is collected from mature male salmon. The collection is typically conducted under sterile conditions using specialized tools and equipment to minimize contamination.

b) Cell Lysis: The collected salmon sperm is treated with gentle lysis buffers to break open the cells and release their contents, including PDRNs. The lysis process should be optimized to minimize DNA degradation and ensure the preservation of intact PDRNs.

c) Filtration and Centrifugation: The lysed sample is passed through sterile filters to remove larger particles, cellular debris, and potential contaminants. The filtrate can then be subjected to gentle centrifugation to pellet down any remaining cellular components.

d) Endotoxin Removal: Endotoxins, which are present in bacterial cell walls, can cause adverse reactions when injected into the body. To ensure the safety of the PDRNs for aesthetic use, endotoxins are typically removed using specialized methods such as endotoxin-binding resins or filtration through sterile filters with defined pore sizes.

e) Chromatography: Chromatography techniques, such as high-performance liquid chromatography (HPLC), can be used to further purify the PDRNs and separate them from other impurities. HPLC purification helps to achieve high purity by separating PDRNs based on their size, charge, or hydrophobicity.

f) Sterilization: To ensure the sterility of the PDRNs for aesthetic use, sterilization methods such as filtration through sterile filters, irradiation, or heat treatment may be applied. These processes eliminate any potential microbial contaminants without degrading the PDRNs.

g) Freeze-Drying: Once purified, the PDRNs can be freeze-dried to convert them into a stable powder form. Freeze-drying helps to extend the shelf life of the product while preserving the integrity and bioactivity of the PDRNs.

It is crucial to follow Good Manufacturing Practices (GMP) and follow appropriate guidelines to ensure the safety, purity, and sterility of the PDRNs for aesthetic use. These processes are usually performed in a controlled environment, such as a certified cleanroom, to minimize the risk of contamination.

IV. MECHANISMS OF ACTION

For Khan (2022), some of the mechanisms of action are important for the treatment with PDRN which improves collagen synthesis.

a) Cellular uptake and intracellular signaling pathways activated by salmon PDRNs

Polydeoxynucleotides (PDNs) derived from salmon have been found to exhibit various cellular uptake and intracellular signaling pathways, leading to beneficial effects on immune responses. Cellular uptake of salmon PDNs is primari-

ly mediated by endocytosis, where the PDNs are internalized into cells via the formation of vesicles. Several studies have shown that the uptakeof PDNs is enhanced in immune cells such asmacrophages, dendritic cells, and B cells.

Once inside the cells, salmon PDNs activate various intracellular signaling pathways. One of the key pathways involved is the Toll-like receptor (TLR) signaling pathway, according to Kawasaki, T and Kawai, T.(2014), particularly TLR9, which recognizes PDNs containing unmethylated CpG motifs.

Binding of PDNs to TLR9 activates downstream signaling molecules such as MyD88, IRAK1, and TRAF6, ultimately leading to the activation of transcription factors like NF-κB and AP-1. This results in the production of pro-inflammatory cytokines, chemokines, and type I interferons, which help initiate and modulate immune responses.

Another important signaling pathway activated by salmon PDNs is the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway. PDNs can activate cGAS, which senses cytoplasmic DNA, leading to the production of cyclic GMP-AMP (cGAMP). cGAMP then binds to STING, triggering the activation of downstream signaling molecules like TBK1 and IRF3, resulting in the production of type I interferons and other immune modulatory molecules.

Overall, the cellular uptake and intracellular signaling pathways activated by salmon PDNs play a critical role in modulating immune responses. These pathways can lead to the production of pro-inflammatory cytokines, type I interferons, and other immune modulatory molecules, ultimately enhancing the immune system's ability to fight against pathogens and regulate immune homeostasis.

a) Stimulation of fibroblast proliferation and differentiation

The mechanism behind the stimulation of fibroblast proliferation and differentiation by PDRNs is believed to involve the activation of various growth factors and signaling pathways. To Veronesi at al.(2017), PDRNs have been found to promote the expression of growth factors like fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), which can stimulate fibroblast proliferation.

Additionally, PDRNs can activate signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase (PI3K) pathway. These pathways play crucial roles in cell proliferation and differentiation, and their activation by PDRNs can enhance fibroblast function.

b) Promotion of collagen and elastin synthesis

Polydeoxyribonucleotides (PDRNs) derived from salmon have been found to promote collagen and elastin synthesis in the skin due to their unique mechanism of action.

PDRNs have the ability to activate various growth factors, such as transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF) (Squadrito, 2017).

These growth factors play a crucial role in the synthesis of collagen and elastin. Activation of these growth factors by PDRNs enhances the signaling pathways involved in collagen and elastin production.

PDRNs also promote the formation of a healthy extracellular matrix, which provides structural support for collagen and elastin fibers. A well-organized extracellular matrix allows for proper alignment and stability of collagen and elastin fibers, resulting in improved synthesis, and PDRNs have vasodilatory effects, meaning they widen blood vessels and improve blood flow to the skin. Improved microcirculation provides essential nutrients and oxygen to the cells involved in collagen and elastin synthesis, thereby enhancing their production.

d)Anti-inflammatory and antioxidant effects of salmon PDRNs

The exact mechanism of action behind the anti-inflammatory and antioxidant effects of salmon polydeoxyribonucleotides (PDRNs) is still being studied. However, several potential mechanisms have been proposed.

PDNs may inhibit the production and release of pro-inflammatory mediators such as cytokines, prostaglandins, and leukotrienes, which are involved in the inflammatory response (KIM, et al. 2021).

Theyhave been shown to modulate immune responses, promoting anti-inflammatory cytokine production and suppressing the activity of inflammatory cells such as macrophages and neutrophils.

Polydeoxyribonucleotides possess antioxidant properties and may scavenge reactive oxygen species (ROS) and free radicals, thus reducing oxidative stress and inflammation.

PDNs can modulate gene expression, including genes involved in inflammation and oxidative stress pathways, thereby regulating the inflammatory and antioxidant response, and may activate specific anti-inflammatory pathways, such as

the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which regulates the expression of antioxidant enzymes.

V- AESTHETIC APPLICATIONS

Salmon-derived Polydeoxyribonucleotides (PDRNs)promote the growth and activity of fibroblasts.Approximately 54,55 fibroblasts are located in the dermal layer, suggesting that PDRNs must be administered directly into this layer to obtain maximum benefits (Khan, 2022). In this case, some applications are:

a)Facial rejuvenation: Use of salmon PDRNs in dermal fillers, mesotherapy, and microneedling

b)Hair restoration: Efficacy of salmon PDRNs in promoting hair growth and preventing hair loss

c)Wound healing: Acceleration of tissue repair and scar reduction with salmon PDRNs

d)Hand and body rejuvenation: Application of salmon PDRNs in addressing age-related skin changes

VI- SAFETY AND SIDE EFFECTS

Salmon polydeoxyribonucleotides (PDRNs) are commonly used in aesthetic treatments for their potential skin rejuvenation benefits. However, evaluating the safety profile of any substance is critical before considering its use in aesthetic procedures. Here is an evaluation of the safety profile of salmon PDRNs and its side effects based on Kim (2021):

a) Clinical Studies: Numerous clinical studies have been conducted to assess the safety and efficacy of salmon PDRNs in aesthetic use. These studies have generally reported minimal adverse effects and a good safety profile.

b) Non-toxic Nature: PDRNs are naturally occurring substances found in various tissues, including salmon DNA. They have been used for many years in medical and aesthetic applications without significant reports of toxicity.

c) Allergic Reactions: Although allergic reactions are rare, they can still occur with the use of salmon PDRNs. Hypersensitivity to fish or other seafood may increase the risk of an allergic reaction. Prior patch testing or checking for allergies beforehand can help identify individuals prone to such reactions.

d)Local Side Effects: Some patients may experience mild local side effects after PDRN injections, such as swelling, redness, pain, or bruising at the injection site. However, these side effects are generally temporary and resolve within a few days.

e)Systemic Side Effects: PDRNs are usually administered locally and have minimal systemic absorption. Consequently, the risk of systemic side effects is minimal.

f)Contamination Risks: The production process of salmon PDRNs needs to adhere to strict quality control measures to minimize the risk of contamination. Proper purification and sterilization methods must be employed to ensure a safe final product.

g)Pregnancy and Breastfeeding: Due to a lack of sufficient research, the use of salmon PDRNs in pregnant or breastfeeding individuals is generally not recommended.

h)Drug Interactions: Salmon PDRNs have not been extensively studied regarding potential drug interactions. Therefore, it is advisable to consult with a healthcare professional to ensure any potential interactions are considered when using PDRNs alongside other medications.

i) Long-Term Safety: Although short-term studies have shown a good safety profile, more long-term studies are needed to evaluate the safety of salmon PDRNs over an extended period.

While salmon polydeoxyribonucleotides (PDRN) have been used in aesthetic medicine for various purposes such as skin rejuvenation and hair loss treatment (khan, 2022), there are a few common side effects and potential adverse reactions that can occur. These include:

a) Localized redness and swelling: Some individuals may experience temporary redness and swelling at the injection site. This is a common side effect that usually subsides within a few hours or days.

b) Bruising: It is possible to develop bruising at the injection site, especially if the procedure involves injecting the PDRN solution into the skin. Bruising typically resolves within a week or two.

c)Itching or skin sensitivity: In some cases, individuals may experience mild itching or skin sensitivity at the injection site. This is usually temporary and should resolve within a few days.

d)Allergic reactions: Although rare, some individuals may develop an allergic reaction to salmon PDRN. Symptoms may include hives, itching, swelling of the face or throat, difficulty breathing, or anaphylaxis. If any allergic symptoms occur, immediate medical attention should be sought.

e)Infection: There is always a risk of infection with any injection-based treatment, including salmon PDRN. Proper sterile techniques should be followed to minimize this risk.

It is important to note that the side effects mentioned above are not exhaustive, and individual responses may vary. It is recommended to consult with a healthcare professional or aesthetic practitioner before undergoing any treatment using salmon PDRN to fully understand the potential risks and benefits.

VII-FUTURE PERSPECTIVES AND CHALLENGES

Salmon polydeoxyribonucleotides (PDRN) are derived from salmon DNA and have been shown to have various biological properties such as anti-inflammatory, wound healing, and tissue regeneration effects.

In terms of future perspectives, PDRN may continue to be explored for their potential applications in aesthetic medicine. Research and development efforts may focus on optimizing the extraction and purification methods to increase their effectiveness and safety. There may also be investigations into new delivery methods for efficient and targeted administration, such as nanoparticles or dermal fillers.

Furthermore, the combination of PDRN with other aesthetic treatments, such as microneedling, laser therapy, or injection with other rejuvenating agents, may be explored to enhance their overall efficacy and provide more comprehensive results. The use of PDRN in combination with stem cell therapy or platelet-rich plasma (PRP) treatments (LEE, 2015) may also be investigated to maximize the regenerative potential.

However, there are several challenges that need to be addressed. Firstly, further clinical studies are required to establish the efficacy and long-term safety of PDRN in aesthetic use. More rigorous research is needed to ascertain the optimal dosage, treatment frequency, and duration for different aesthetic indications.

Additionally, the cost-effectiveness of PDRN treatments may be a concern, as the extraction and purification process can be expensive. This may limit its widespread availability and accessibility for patients seeking aesthetic treatments.

Lastly, there may be regulatory challenges and ethical considerations surrounding the sourcing of salmon DNA for PDRN extraction. Ensuring sustainable and responsible sourcing practices will be crucial to address any potential environmental or ethical concerns.

VIII- CONCLUSION

In summary, salmon-derived PDNs are composed of deoxyribonucleotide monomers arranged in a specific sequence to form a linear, single-stranded chain. The specific functional properties of PDNs are determined by their sequence and length, and ongoing research aims to uncover their full potential in various fields.

It is important to note that the use of nucleic acid-based compounds in aesthetic medicine is still evolving, and more research is being conducted to fully understand their potential benefits and limitations. Additionally, these compounds should only be used under the supervision of trained medical professionals to ensure safety and efficacy.

Salmon-derived PDRNs have demonstrated a generally good safety profile in aesthetic use. However, it is crucial for healthcare professionals to conduct thorough evaluations and follow established guidelines to ensure patient safety and minimize potential risks.

In conclusion, the future perspectives of salmon PDRN in aesthetic use hold promise for skin rejuvenation even combined with collagen biostimulator and hair growth.

However, further research, clinical studies, and cost-effectiveness evaluation are needed to fully establish their efficacy, safety, and practical applications in aesthetic medicine.

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