www.ijprems.com
editor@ijprems.com

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)
(Int Peer Reviewed Journal)
Vol. 04, Issue 11, November 2024, pp : 2096-2100

e-ISSN : 2583-1062
Impact Factor : 7.001

CLINICAL USE AND PHARMACOLOGICAL ACTIVITY OF PDRN (POLYDEOXYRIBONUCLEOTIDE)

Shrihari A. Jadhav[1], Yugandhara P. Shingade[2], Dr. Vijaysinhg U. Sable[3], Dr Rani M. Mhetre[4]

[1]Lokmangal college of pharmacy, wadala, Solapur, Maharashtra, India.

[2]Assistant professor, Lokmangal college of pharmacy, wadala, Solapur, Maharashtra, India.

[3,4]Associate professor Lokmangal college of pharmacy, wadala, Solapur, Maharashtra, India.

ABSTRACT

Lippia graveolens, commonly known as Mexican oregano, has been traditionally used in folk medicine for its medicinal properties. This review aims to summarize the clinical use and pharmacological activity of L. graveolens.

- Anti-inflammatory and antioxidant effects
- Antispasmodic and analgesic properties
- Potential anticancer and immunomodulatory activities Clinical studies have supported the use of L. graveolens for:
- Gastrointestinal disorders (e.g., dyspepsia, diarrhea)
- Respiratory issues (e.g., bronchitis, asthma)
- Skin conditions (e.g., acne, wounds)
- Antimicrobial applications (e.g., mouthwash, wound healing)

The pharmacological activity of L. including thymol, carvacrol, and beta-caryophyllene. While further research is needed to fully elucidate its clinical efficacy and safety, L. graveolens holds promise as a complementary therapy for various health

1. INTRODUCTION

Over the past decade, pharmacologists have intensely investigated the pharmacological properties of substances produced by living organisms. DNA-derived drugs, such as PDRN (polydeoxyribonucleotide) and defibrotide, have shown promising therapeutic potential. Despite sharing a common DNA origin, these two drugs differ significantly in terms of DNA source, molecular weight, and manufacturing processes, resulting in distinct pharmacological profiles, mechanisms of action, and clinical effects. While defibrotide has received comprehensive review in recent literature (Pescador et al., 2013; Richardson et al., 2013), PDRN has not been revisited since 2009 (Altavilla et al., 2009), highlighting the need for an updated examination of its properties and applications.

PDRN Chemistry

PDRN is a proprietary DNA-derived drug extracted from salmon trout or chum salmon sperm DNA, The purification process involves high-temperature extraction, yielding >95% pure active substance with inactivated proteins and peptides, ensuring product safety and eliminating immunological side effects.

Key differences between PDRN and defibrotide:

- -Source: PDRN (salmon trout/chum salmon sperm DNA), defibrotide (porcine intestinal mucosal DNA)
- -Molecular weight: PDRN (50-1,500 KDa), defibrotide (16.5 ± 2.5 KDa)
- -Purification process: PDRN (high-temperature extraction), defibrotide (not specified)

The use of spermatozoa as raw material minimizes contamination risks from peptides, proteins, and lipids, guaranteeing high-purity DNA.

PDRN Pharmacokinetics

Pharmacokinetic studies in rats and humans revealed that PDRN exhibits:

Rat Study (8 mg/kg, intraperitoneal)

- Rapid absorption: measurable levels at 15 min, peak at 1 h
- High bioavailability: 90%
- Half-life: 3 h (dosage-independent)
- Plasma levels decreased progressively, still detectable at 6 h
- Distribution dependent on tissue blood flow
- No liver metabolism; degraded by plasma DNA nucleases and cell membrane-bound nucleases

www.ijprems.com
editor@ijprems.com
INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)
(Int Peer Reviewed Journal)
Vol. 04, Issue 11, November 2024, pp : 2096-2100
e-ISSN : 2583-1062
Impact Factor : 7.001

- Excreted primarily in urine (~65%) and feces

Human Study (5.625 mg, intramuscular)

- Similar pharmacokinetic profile to rat study
- Peak levels at ~1 h
- Half-life: ~3.5 h
- Bioavailability: 80-90%

PDRN's pharmacodynamics effects outlast its plasma half-life due to its degradation into nucleosides and nucleotides, which bind to the adenosine A2A receptor

Pharmacological Properties of PDRN:

Experimental in vitro Studies Supporting The Mode of Action :-

PDRN, a DNA-derived drug, interacts with adenosine A2A receptors, modulating inflammation, oxygen consumption, ischemia, cell growth, and angiogenesis. Studies demonstrate PDRN's potential therapeutic effects:

1. Cell growth and proliferation: PDRN stimulates human skin fibroblasts and osteoblasts, promoting DNA synthesis and repair.
2. Tissue regeneration: PDRN protects cartilage, reducing extracellular matrix degradation and synergizing with glucosamine.
3. DNA repair: PDRN enhances repair of UV-induced DNA damage in human dermal fibroblasts.

Key findings:-

PDRN acts on adenosine A2A receptors, confirmed by antagonist studies.

-PDRN generates nucleotides and nucleosides, contributing to DNA formation

-PDRN promotes cell growth, proliferation, and differentiation in various cell.

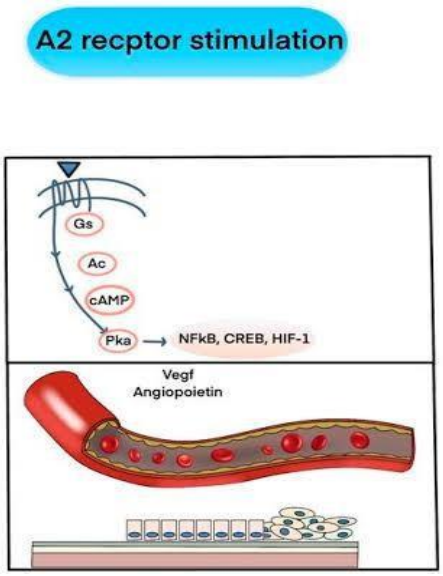
Therapeutic implications:-

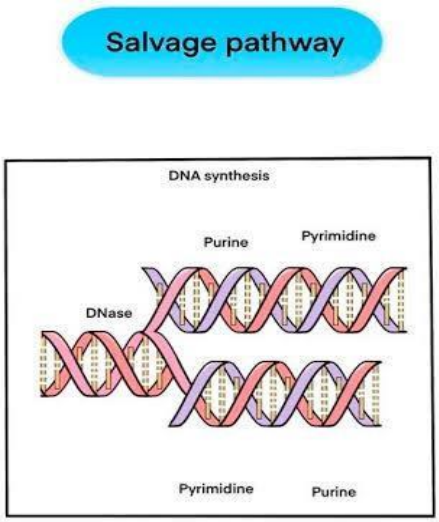
Regenerative medicine: PDRN may aid in cartilage repair and tissue regeneration

-Dermatology: PDRN protects against UV-induced DNA damage.

-Orthopedics: PDRN may enhance bone growth and repair.

Research highlights PDRN's potential as a pro-drug, providing active deoxyribonucleotides, nucleosides, and bases for salvage pathways, supporting DNA synthesis and rapair





2. MATERIAL AND METHOD

Experimental Design

The Üsküdar University Ethics Committee accepted this experimental animal study and verified that all experiments were carried out in compliance with applicable rules and regulations (Decision No. 2016-07). In this investigation, 30 male adult Wistar albino rats, ages 5–7 months, weighing 220–275 g, were employed. Rats were kept in a typical laboratory during the trial period, fed, and kept in the following conditions: 20–24°C, 50%–55% relative humidity, 12-hour light/12-hour dark, noise-free, and without any restrictions on liquid or nutrients.

www.ijprems.com
editor@ijprems.com

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)
(Int Peer Reviewed Journal)
Vol. 04, Issue 11, November 2024, pp : 2096-2100

e-ISSN : 2583-1062
Impact Factor : 7.001

Surgical procedure

Each experimental rat received its own set of surgical tools, which were prepared in a sterile cover. A submuscular injection of xylazine hydrochloride (5 mg/kg; Rompun, Bayer, Germany) and ketamine hydrochloride (50 mg/kg; Ketalar, Pfizer, USA) was used to put the rats to sleep. By applying a painful stimulus to the foot and evaluating the corneal reflex, the anesthetic depth was managed. Each rat was shaved by applying a depilatory lotion to its right flank after the anesthetic depth of the subject animals was confirmed. All rats received preoperative intramuscular cefazolin sodium (25 mg/kg; cefazolin, Mustafa Nevzat, Turkey) as an antibacterial prophylactic.Using a 21-gauge insulin injector, group 2 (HA group) received a single intra-articular injection of HA (12 mg/0.05 cc, 1.0–1.5 106 Dalton; Orthoflex, Atlantis, Turkey) into the right knee. A single intra-articular injection of 50 l/0.05 cc cc of 0.9% NaCl was given to the right knee of group 3 (the saline group) using a 21-gauge insulin injector. Rats were sacrificed by beheading four weeks after the treatment. A distal femur and proximal tibia

were removed together with the knee joint and examined histopathologically after a midline osteotomy was carried out through the femur and tibial diaphysis.

Histoparhological Evaluation -

Before being evaluated, the specimens were kept in pathological cups with 10% formalin. After being assigned a random number, the specimens were forwarded to the pathology division. After a week of fixation, the specimens were decalcified for five days (ShandonTM TBD-2TM, Thermo Scientific, USA). Following decalcification, 2-mm specimen sections were taken from the tissues to evaluate the preserved tissue orientation, joint space, and synovial membranes. After three hours of additional washing to remove any remaining water, the samples were put in an automatic tissue monitoring device (Shandon Excelsior ES, USA) for thirteen hours.Multiple evaluations were conducted at various time points in order to lower the intraobserver error rate. Mankin scores were used to evaluate the results. Four parameters make up the Mankin scoring system: cellular alterations (0–3 points), safranin-O staining pattern (0–4 points), structural integrity (0–6 points), and tidemark continuity (0–1 points). A score of 0 indicates that the normal structure remains unchanged, whereas a value of maximum indicates that the OA results have progressed.

Statistical Analysis -

For statistical analysis, the Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) software was utilized.The Mann-Whitney U-test was used to determine which group was

different. When comparing quantitative data and descriptive statistical methods , the Mann- Whitney U-test was used to compare the results of the Kruskal-Wallis test and discriminant groups. Fisher's exact test and the Fisher-Freeman-Halton test were used to compare the qualitative data.. Significance was assessed at p-values less than 0.05 and less than 0.001.

Cell viability test -

1) Cell Counting Kit-8 assay

   Cell Counting Kit-8 was used to assess the vitality of human PDL cells kept in each medium (CCK-8; Dojindo Molecular Technologies, Kumamoto, Japan). PDL cells were first seeded into a 96-well plate at a density of 5×10^2 cells/well using 200 µL of growth medium. The following prepared solutions were treated after the culture media were removed during a 24-hour incubation period: (a) HBSS; (b) 10 µg/mL PDRN; (c) 25 µg/mL PDRN; (d) 50 µg/mL PDRN; (e) 100 µg/mL PDRN; and (f) tap water. In order to replicate the extraoral situation, the cells were kept in each solution for 0, 1, 3, 6, 12, and 24 hours. They were also exposed to room temperature and a typical atmospheric environment.Then, each plate received 20 µg of CCK-8 solution. A Benchmark Plus Multi- plate Spectrophotometer (Bio-Rad, Hercules, CA, USA) was used to measure the optical density at 450 nm (A450) following two hours of incubation at 37°C in order to assess the

   viability of the cells. The following formula was used to get the relative cell viability (%): ÷ (A450 [control] ÷ (A450 [blank]) × 100% (A450 [treatment] – A450 [blank]). Three samples were used in each experiment, and the assays were run in triplicate.

2) Live/Dead assay

   The Mammalian Cell Cytotoxicity/LIVE/DEAD Viability Kit (Invitrogen,paisley UK)was used to assess the viability of human PDL cells kept in each medium. In a 12-well plate, PDL cells were seeded at a density of 2 × 104 cells/well using 2 mL of growth medium.

   The pre-made solutions (HBSS, 10 µg/mL PDRN, 25 µg/mL were treated for 0, 1, 3, 6, 12,

   and 24 hours after the culture medium were removed during a 24-hour incubation period. The dye reagent was made by mixing 10 mL of Dul-becco's phosphate-buffered saline (Gibco BRL, Life Technologies, Grand Island, NY, USA) with 5 µL of 2 µM calcein AM and 20 µL of 2 mM ethidium homodimer-1.Vortexing the resultant solution made sure it was well mixed. Each plate's storage media were taken out, and the staining agent was allowed to sit at room

temperature for ten minutes. Fluorescence microscopy (IX71; Olympus, Tokyo, Japan) was used three times at various locations to get a fluorescence microphotograph of both live and dead PDL cells in each storage media. The number of live cells ÷ (The quantity of living cells + the number of dead cells) × 100 was used to compute the relative cell viability (%). All assays were performed three times.

3. RESULT

Following the surgical operation, the experimental rats showed no signs of infection or weight loss.The Mankin scoring system evaluation findings for each study group are displayed. All groups had significantly different total Mankin scores (p ¼ 0:001). The PDRN and HA groups' overall Mankin scores were considerably lower than the saline group's, according to bilateral comparisons conducted to determine whether group displayed a difference.Additionally, there was.The PDRN and HA groups' structural integrity was considerably worse than that of the saline group ($p < 0:01$ and $p < 0:05$, respectively), per bilateral comparisons done to determine whether group had a difference. Additionally, the structural integrity of the PDRN group was considerably worse than that of the HA group ($p < 0:01$).The three groups differed considerably in terms of cellular alterations, safranin-O staining, and tidemark continuity (p ¼ 0:001). Significantly less cellular change was seen in the PDRN and HA groups than in the saline group, per bilateral comparisons done to determine which groupdisplayedadifference

($p < 0:01$ and $p < 0:05$, respectively). the PDRN group displayed noticeably fewer cellular alterations ($p < 0:01$;

4. DISCUSSION

Following the incubation of the individual tested drugs separately and in combination, the C0L11AI gene expression was reduced in this experiment. Collagen XI is recognized as a member of the fibrillar collagen group; it is arranged in cartilage fibrils with collagen II and IX and is made up of three distinct chains, each of which is transcribed by a separate gene. Its function is to regulate the size of the offibril. Additionally, it is linked to the extracellular matrix's eparan and dermatan sulphate, which helps to stabilize it and preserve tissue integrity.To understand the behavior seen in this study, more experiments are required. Metalloproteinases (MMPs) are recognized as the primary enzymes in charge of tissue remodeling and ECM breakdown. Although little is known about how MMPs work in biology and pathology, some of their biological functions appear contradictory; in reality, they may have pro- or anti-inflammatory or pro- or anti-angiogenic actions.Although the domain organization of MMP-3, also known asstromelysine, is comparable to that of collagenases, it is unable to cleave interstitial collagens.

5. REFERENCE

[1] Akman Ş, Şen C. The efficacy of intraarticular sodium hyaluronate injection following arthroscopic. Acta Orthop Traumatol Turc 35:107–110, 2001.

[2] Anthony D, Bruce P. Global economic and health care burden of musculoskeletal disease. World Health Org 81:646–656, 2003.

[3] Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 18(2):CD005321 2005.

[4] Bitto A, Polito F, Irrera N, D'Ascola A, Avenoso A, Nastasi G et al., Polydeoxyribonucleotide reduces cytokine production and the severity of collagen-induced arthritis by stimulation of adenosine A((2)AÞ receptor. Arthritis Rheum 63:3364–3371, 2011.

[5] Chung KI, Kim HK, Kim WS, Bae TH. The effects of polydeoxyribonucleotide on the survival of random pattern skin flaps in rats. Arch Plast Surg 40:181–186, 2013.

[6] Dallari D, Sabbioni G, Del Piccolo N, Carubbi C, Veronesi F, Torricelli P et al., Efficacy of ıntra-articular polynucleotides associated with hyaluronic acid versus hyaluronic acid alone in the treatment of knee osteoarthritis: A randomized, double-blind. Controlled Clinical TrialClin J Sport Med 30(1):1–7, 2020.

[7] Fonsi M, El Amrani AI, Gervais F, Vincent P. Intraarticular hyaluronic acid and chondroitin sulfate: Pharmacokinetic ınvestigation in osteoarthritic rat models. Curr Ther Res Clin Exp 92:100573, 2019.

[8] Galeano M1, Bitto A, Altavilla D, Minutoli L, Polito F, Calò Met al., Polydeoxyribonucleotide stimulates angiogenesis and wound healing in the genetically diabetic mouse. Wound Repair Regen 16:208–217, 2008.

[9] Gennero L, Denysenko T, Calisti GF, Vercelli A, Vercelli CM, Amedeo Set al., Protective effects of polydeoxyribonucleotides on cartilage degradationin experimental cultures. Cell Biochem Funct 31(3):214–227, 2013.

[10] Giarratana LS, Marelli BM, Crapanzano C, De Martinis SE, Gala L, Ferraro M et al., A randomized doubleblind clinical trial on the treatment of knee osteoarthritis: The efficacy ofpolynucleotides compared to standard hyaluronian viscosupplementation. Knee 21:661–668, 2014.

[11] Guizzardi S, Galli C, Govoni P, Boratto R, Cattarini G, Martini D et al., Polydeoxyribonucleotide (PDRN)promotes human osteoblast proliferation: A new proposal for bone tissue repair. Life Sci 73:1973–1983, 2003.

[12] Hauk L. Treatment of knee osteoarthritis: A clinical practice guideline from the AAOS. Am Fam Phys 89:918–920, 2014.

[13] Hayami T, Pickarski M, Zhuo Y, Wesolowski GA, Rodan GA, Duong LT. Characterization of articular cartilage and subchondral bone changes in the rat anterior cruciate ligament transection and meniscectomized models of osteoarthritis. Bone 38(2):234–243, 2006

[14] Pester JK, Stumpfe S, Steinert S, Marintschev I, Aurich M, Hofmann GO. BMP-

[15] 2 shows characteristic extracellular patterns in osteoarthritic cartilage: A preliminary report. GMS Interdiscip Plast Reconstr Surg DGPW 2: Doc09, 2013.

[16] Phillips M, Vannabouathong C, Devji T, Patel R, Gomes Z, Patel A et al., Differentiating factors of intra-articular injectables have a meaningful impact on knee osteoarthritis outcomes: A network meta-analysis. Knee Surg Sports

[17] Traumatol Arthrosc 28(9):3031–3039, 2020, doi: 10.1007/s00167-019-05763-1.Rubegni P, De Aloe G, Mazzatenta C, Cattarini L, Fimiani M. Clinical evaluation of the trophic effect of polydeoxyribonucleotide (PDRN) in patients undergoing skin explants. A Pilot Study. Curr Med Res Opin 17:128–131, 2001.

[18] Siddiqui F, Karkare S : Storage media for an avulsed tooth: nature to the rescue. Br J Med Health Res, 1:1- 10, 2014. Poi WR, Sonoda CK, Martins CM, Melo ME, Pellizzer EP, de Mendonca MR, Panzarini SR : Storage media for avulsed teeth: a literature review. Braz Dent J, 24: 437-445, 2013.

[19] Rajakeerthi R, Nivedhitha MS : Natural Product as the Storage median avulsed tooth - A Systematic Review. Cumhur Dent J, 22:249-256, 2019.

[20] Soloman L. Clinical features of osteoarthritis. in Kelley WN, Harris ED, Ruddy S, Sledge CB (eds.), Textbook of Rheumatology. WB Saunders Company, Philadelphia, pp. 1383–1393, 1997.

[21] Tolba YM, Omar SS, Nagui DA, Nawwar MA. Effect of high molecular weight hyaluronic acid in treatment of osteoarthritic temporomandibular joints of rats. Arch Oral Biol 110:104618, 2020

[22] Vuoristo M. Minor cartilage collagens. Characterization ofthe human COL9AI, COL9A2 and COLlIA2 genes and the mouse COLlIA2 gene. Identification of a mutation in the COLlIA2 gene in a family with non-ocular Stickler syndrome. Oulu University Press 2003.

[23] Lee AS, Ellman MB, Yan D, Kroin JS, Cole BJ, van Wijnen AJ, 1m HJ. A current review of molecular mechanisms regarding osteoarthritis and pain. Gene 2013; 527:440-47.

[24] Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res 2006; 69:562-73.