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NANO GEL BASED CO-DELIVERY OF DICLOFENAC SODIUM AND LUTEOLIN: A PROMISING THERAPEUTIC STRATEGY FOR SPINAL MUSCULAR ATROPHY

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ABSTRACT

Spinal muscular atrophy (SMA), a progressive neuromuscular disorder characterized by degeneration of lower motor neurons as a result of SMN1 gene deletion and inadequate SMN protein production. Neuroinflammation, oxidative stress, and mitochondrial dysfunction further expedite muscle atrophy and motor decline. Diclofenac sodium is a widely used NSAID, exhibits anti-inflammatory and neuroprotective activity; however, its oral administration is limited due to gastrointestinal toxicity and poor CNS penetration. Luteolin is a naturally occurring flavonoid with strong antioxidant and neuroprotective properties, looks promising in modulating inflammatory pathways, improving mitochondrial function, and supporting neuronal regeneration. Nanogel-based drug delivery offers enhanced stability, controlled release, improved tissue penetration, and reduced systemic toxicity for CNS-targeted therapy. This review explores the mechanistic benefits of diclofenac sodium and luteolin in SMA pathology and highlights the potential synergistic role of their co-delivery via nanogel technology. Such a combined nanogel formulation may provide targeted neuroprotection, reduced inflammation, and improved patient compliance, representing a promising future therapeutic strategy for SMA management.

KEYWORDS: Spinal muscular atrophy (SMA), Diclofenac sodium, Luteolin, Neuroinflammation, Neuroprotection, SMN1 gene deletion.

1. INTRODUCTION

Spinal muscular atrophy (SMA) is a neurological illness characterized by a gradual loss of motor neurons, muscle atrophy, and physical impairment. Typical therapy techniques include symptom management, inflammation control, and neuroprotection. NSAIDs such as diclofenac sodium have considerable anti-inflammatory and analgesic properties, but severe gastrointestinal responses complicate oral administration. Luteolin, which is structurally identified as 3′,4′,5,7-tetrahydroxyflavone, is a naturally occurring flavonoid that is abundant in many food plants and traditional medicinal herbs. Its numerous pharmacological actions, including antioxidant, anti-inflammatory, anticancer, and neuroprotective effects, are mediated through the regulation of key signalling pathways such as NF-κB, MAPKs, and STAT3, and have attracted significant interest. However, poor water solubility, limited oral bioavailability, and quick metabolism hinder its practical translation. To improve its stability and therapeutic efficiency, substantial research has been conducted into improved delivery technologies, such as hydrogels and nano-scale carriers. Advancements in drug delivery technologies, such as nanogels, have led to increased interest in combining medications with neuroprotective flavonoids like luteolin to enhance benefits and outcomes.

1.1 Diclofenac Sodium: Function and Constraints

A common non-steroidal anti-inflammatory medicine (NSAID) for pain and inflammation is diclofenac sodium (DS). Limited CNS penetration and gastrointestinal side effects are linked to standard oral Diclofenac Sodium. Nanogel formulations reduce systemic adverse effects by increasing stability, extending release, and enabling transdermal or localized distribution. In numerous

investigations, diclofenac sodium-loaded nanogels have demonstrated encouraging outcomes for enhanced tissue targeting and a sustained analgesic impact. These findings may be applied to the treatment of neuroinflammatory and neuromuscular disorders.

1.2. Diclofenac Sodium: Anti-Inflammatory and Neuroprotective Effects

Diclofenac sodium has shown neuroprotective properties relevant to neurodegenerative illnesses, perhaps lowering neuronal inflammation and enhancing motor function, in addition to its well-established effectiveness for pain and inflammation. Research shows that long-term use of diclofenac reduces cognitive deterioration in some groups. Diclofenac delivered using nanogel preserves good therapeutic efficacy, prevents stomach injury, and regulates plasma drug levels.

2. MECHANISM OF ACTION OF DICLOFENAC SODIUM IN SMA

Diclofenac's primary mechanism of action is the inhibition of cyclooxygenase enzymes, particularly COX-2, which lowers prostaglandin synthesis and, consequently, inflammation and pain signals that are essential to the pathophysiology of SMA and other neurodegenerative diseases.

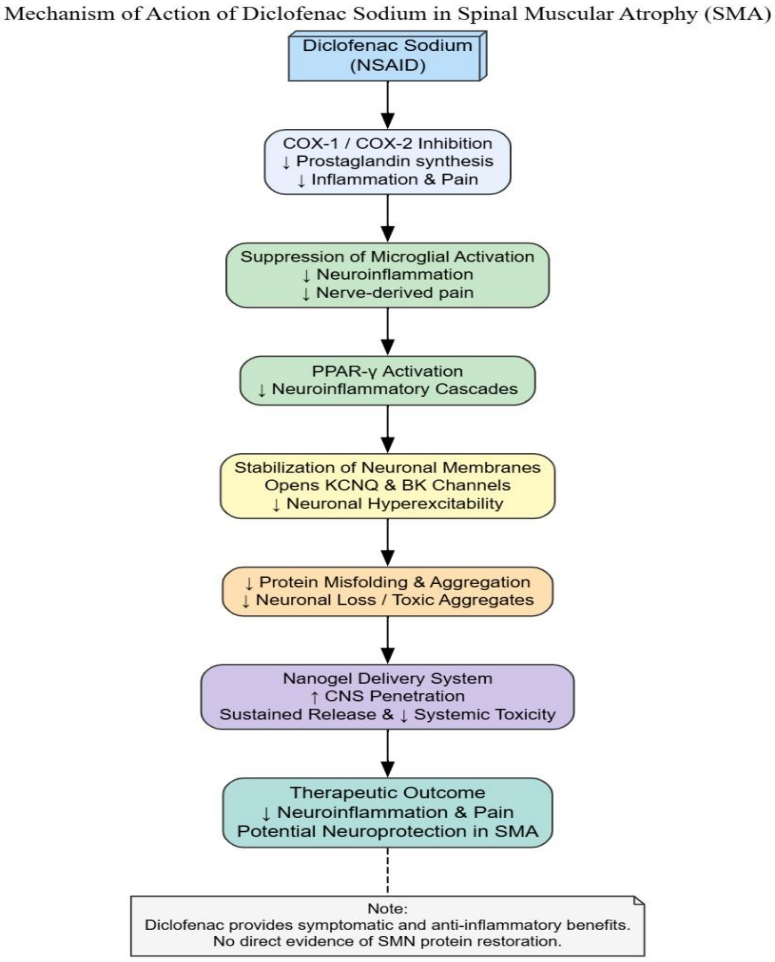
Suppression of Microglia Activation: Recent studies demonstrate that diclofenac sodium at the spinal cord level reduces the activation of microglia (the CNS immune cells), hence lowering neuroinflammation and nerve-derived pain mechanisms, which are extremely significant in SMA.

PPAR-γ Activation: Diclofenac has synergistic effects by activating peroxisome proliferator-activated receptor-γ (PPAR-γ), further adding to the inhibition of neuroinflammatory cascades.

Stabilization of Neuronal Membranes: Diclofenac can open KCNQ- and BK-potassium channels, leading to neuronal hyperpolarization, which lowers neuronal hyperexcitability found in chronic neuropathic pain.

Decrease in Protein Misfolding and Aggregation: Diclofenac has demonstrated the capacity to prevent the aggregation of neurotoxic amyloid proteins, which could be advantageous in SMA and other disorders involving the loss of neurons and protein misfolding.

Benefits of Nanogel Delivery: When compared to oral administration, nanogel formulations improve medication penetration to neural tissues, offer sustained drug release, sustain a longer therapeutic effect, and lower systemic toxicity.



Abbreviation

PPARγ - peroxisome proliferator-activated receptor, **KCNQ** - potassium voltage-gated channel subfamily Q, **BK channel** - Big Potassium channel, **SMN** - survival motor neuron, **SMA** - Spinal muscular atrophy, **COX-1** - Cyclooxygenase-1, **COX-2** - Cyclooxygenase-2

3. LUTEOLIN

Luteolin is a naturally occurring flavonoid that is extensively present in fruits, vegetables, and medicinal herbs, and it has been studied for its diverse pharmacological properties, including anti-inflammatory, antioxidant, and neuroprotective effects. Its eventuality for use in neurological diseases, including spinal muscular atrophy (SMA), is attracting additional exploration interest due to these properties.

Luteolin, also known as 3',4',5,7-tetrahydroxyflavone, is a yellow crystalline chemical that can be found in a variety of plants, including artichokes, celery, broccoli, parsley, and herbs. Its structure, which enables it to interact with and control signaling pathways linked to oxidative stress and inflammation, is the source of its biological activity. First discovered in 1829, luteolin has a strong antioxidant potential and inhibits oxidative damage and inflammatory mediators at the cellular level.

4. LUTEOLIN USES IN SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy is an inherited neurodegenerative complaint characterized by progressive muscle wasting and weakness. Research has explored luteolin's neuroprotective implicit; however, substantially preclinical as a remedial intervention in neuromuscular conditions.

Luteolin demonstrates neuroprotective and anti-inflammatory properties, which are applicable to SMA, where motor neuron survival and protection against neuroinflammation are crucial therapeutic targets.

Recent studies have indicated that co-administration of luteolin with other neuroprotective agents promotes neuronal rejuvenescence and mitigates inflammation in models of spinal cord injury, which shares mechanistic imbrication with SMA, especially regarding neuroinflammation and muscle atrophy.

Luteolin ameliorates muscle atrophy in preclinical models by perfecting mitochondrial quality control, reducing oxidative stress, and enhancing energy metabolism, mechanisms potentially salutary for SMA cases who suffer muscle atrophy secondary to motoneuron degeneration.

Experimental patents suggest that luteolin or luteolin-grounded compositions may support neuromuscular function and could be considered as an adjunct in the treatment of neuromuscular movement diseases such as SMA, but robust clinical trial substantiation is still lacking.

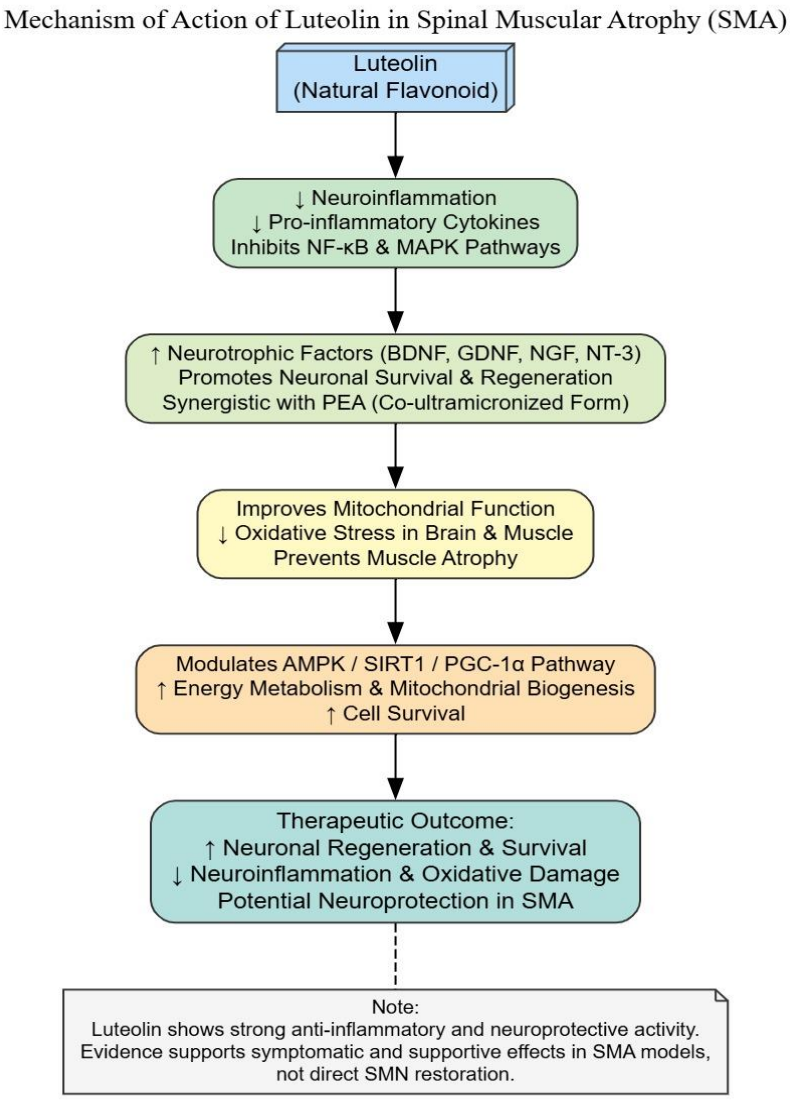
5. MECHANISM OF ACTION OF LUTEOLIN IN SMA

According to research, luteolin functions through several mechanisms related to SMA, including: Reducing neuroinflammation, a major aspect of SMA disease, by downregulating inflammatory signalling cascades and blocking the release of pro-inflammatory cytokines.

Encouraging the development of neurotrophic factors and neuronal regeneration, such as elevated brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor, nerve growth factor, and neurotrophin-3, all of which enhance the survival and regeneration of neurons following spinal cord injury. This has been demonstrated especially when luteolin and palmitoyl ethanol amide are combined (in co-ultra micronized form); nonetheless, luteolin is partially responsible for the neuroprotective impact.

Improving mitochondrial function and lowering oxidative stress in brain and muscle tissues to alleviate mitochondrial dysfunction and muscle atrophy, all of which are strongly associated with the development of SMA.

Modifying signalling networks related to energy metabolism and cell survival, particularly the AMPK/SIRT1/PGC-1α pathway, which protects skeletal muscle and maybe brain tissues by lowering oxidative stress and enhancing mitochondrial quality control.



Abbreviation

NF-κB - Nuclear Factor kappa-light-chain-enhancer of activated B cells, **MAPK - Mitogen-activated protein kinase, BDNF -** Brain-Derived Neurotrophic Factor, **GDNF** - Glial cell line-derived neurotrophic factor, **NGF** - Nerve Growth Factor, **NT-3** - Neurotrophin-3, **AMPK** - AMP-activated protein kinase, **SIRT1** - sirtuin 1 (Silent information regulator 1), **PGC-1α** -Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha.

6. FLOW CHART: PATHOPHYSIOLOGY OF SPINAL MUSCULAR ATROPHY

Step 1: Genetic cause

Homozygous deletion or mutation in the SMN1 gene

↓

Step 2: Reduced functional protein production

Significantly reduced production of full-length, functional survival motor neuron (SMN) protein (The number of SMN2 copies influences severity by producing a small amount of functional SMN)

↓

Step 3: Impaired cellular function

Insufficient SMN protein for essential cellular functions

↓

Step 4: Selective Neuronal Dysfunction

Motor neurons, particularly lower motor neurons in the anterior horn of the spinal cord, are highly vulnerable (SMN protein is critical for motor neuron development, survival, and axonal function)

↓

Step 5: MOTOR NEURON DEGENERATION

Progressive degeneration and death of lower motor neurons (anterior horn cells)

↓

Step 6: loss of innervation

Motor neurons fail to transmit nerve signals to skeletal muscles

↓

Step 7: Muscular Symptoms

Denervation leads to muscle weakness, atrophy (wasting), and hypotonia (low muscle tone)

↓

Step 8: clinical manifestations

Progressive paralysis, difficulty with movement, feeding /swallowing difficulties, and respiratory failure

7. NANOGEL TECHNOLOGY IN CNS DISORDERS

Nanogel drug delivery systems offer advanced options for CNS-targeted therapy due to their ability to cross the blood-brain and blood-spinal cord barriers, achieve controlled release, and protect labile compounds. In various preclinical studies, nanogels loaded with anti-inflammatory agents reduced neuroinflammation, promoted neuronal repair, and improved outcomes in models of spinal cord and neurodegenerative diseases. The biocompatibility and customizable surface properties of nanogels further enable combination therapy, such as co-delivery of diclofenac sodium and luteolin.

8. BENEFITS AND FORMULATION OF NANOGEL

Diclofenac sodium nanogels are formulated using biocompatible polymers (Eudragit S-100, Carbopol 940) and stabilizers, such as glycerine, through modified emulsification-diffusion processes. Usually, these nanogels show:

The 20–200 nm particle size range is perfect for avoiding quick kidney clearance and preserving an extended plasma half-life.

Prolonged drug release profiles (up to 8 hours, with nearly full release in optimal formulations) and high entrapment efficiency (>74%).

Because of their stability and skin compatibility (pH 7–7.3), they can be applied transdermally with little chance of causing systemic toxicity or skin irritation.

Diclofenac sodium is delivered by a transdermal nanogel method that has improved bioavailability, avoids first-pass metabolism, and regulates release kinetics by matrix polymer concentration.

9. COMBINATION TREATMENT: LUTEOLIN NANOGEL AND DICLOFENAC SODIUM

9.1. Synergistic Effect: Diclofenac sodium and luteolin combined in a nanogel technology provide a dual-action immune protective and anti-inflammatory treatment that may be useful for SMA. While luteolin promotes neuronal function and lowers neuroinflammation, diclofenac lessens pain and inflammation.

9.2. Controlled Release and Safety: Nanogels prevent side effect-causing plasma peaks, control medication release rates, and maintain long-term effectiveness. In preclinical models, skin tolerance tests of optimized nanogels (such as those containing glycerine and the right amount of polymer) have shown no signs of toxicity or irritation.

9.3. Stability and Patient Compliance: This approach reduces the need for frequent dosing, guarantees consistent medication administration, and improves patient compliance—all of which are especially beneficial for long-term conditions like SMA.

10. APPLICATION PROSPECTS FOR SMA

Diclofenac sodium may be able to address the neuroinflammatory aspects of SMA pathology, despite the fact that there is currently little study on the direct combination of Diclofenac Sodium and luteolin in a nanogel for SMA.

Luteolin may have antioxidant and neuroprotective properties.

Targeted CNS delivery made possible by nanogel delivery may be important for both adult and pediatric SMA patients, improving safety and effectiveness.

11. CONCLUSION

Diclofenac sodium and luteolin each possess distinct yet complementary pharmacological actions that address key mechanisms underlying SMA pathology, including neuroinflammation, oxidative stress, and neuronal degeneration. Limitations related to poor bioavailability, systemic toxicity, and inadequate CNS targeting can be significantly minimized through nanogel-based delivery systems. A combined nanogel formulation offers controlled drug release, enhanced tissue penetration, reduced adverse effects, and improved therapeutic efficiency. Although direct evidence in SMA is still limited, existing preclinical findings strongly support the potential of diclofenac–luteolin nanogels as an innovative and effective therapeutic approach. Further experimental and clinical investigations are essential to validate this promising strategy for SMA management.

REFERENCES

1. Stavarachi M, Apostol P, Toma M, Cimponeriu D, Gavrila L. Spinal muscular atrophy disease: a literature review for therapeutic strategies [Internet], 2010.
2. Brogden RN, Heel RC, Pakes GE, Speight TM, Avery GS. Diclofenac sodium. Drugs [Internet], Jul 1, 1980; 20(1): 24–48.
3. Nair B, Taylor-Gjevre R. A review of topical diclofenac use in musculoskeletal disease. Pharmaceuticals [Internet], Jun. 11, 2010; 3(6): 1892–908.
4. Satya Lakshmi S, Sowjanya P, Kumari PVK. Formulation and characterization of diclofenac sodium nanogel for controlled drug release. Biosciences Biotechnology Research Asia [Internet], Sep. 30, 2024; 21(3): 967–77.
5. Talele S, Nikam P, Ghosh B, Deore C, Jaybhave A, Jadhav A. A Research Article on Nanogel as a Topical Promising Drug Delivery for Diclofenac Sodium. Indian Journal of Pharmaceutical Education and Research [Internet], Dec. 30, 2017; 51(4s): s580–7.
6. S L, B T, S K, K VS, P P, Ch S, et al. Application of nanogel as a topical drug delivery vehicle for diclofenac sodium. Journal of Innovations in Applied Pharmaceutical Science (JIAPS) [Internet], Apr. 16, 2024; 32–8.

7. Zhang Y, Yang D, Shuai B, Ding H, Yang J, Wang J, et al. Diclofenac sodium nanomedicine results in pain relief and differential expression of the RNA transcriptome in the spinal cord of SNI rats. International Journal of Pharmaceutics [Internet], May 29, 2024; 659: 124276.
8. Stuve O, Weideman RA, McMahan DM, Jacob DA, Little BB. Diclofenac reduces the risk of Alzheimer's disease: a pilot analysis of NSAIDs in two US veteran populations. Therapeutic Advances in Neurological Disorders [Internet], Jan. 1, 2020; 13: 1756286420935676.
9. Stopschinski BE, Weideman RA, McMahan D, Jacob DA, Little BB, Chiang HS, et al. Microglia as a cellular target of diclofenac therapy in Alzheimer's disease. Therapeutic Advances in Neurological Disorders [Internet], Jan. 1, 2023; 16: 17562864231156674.
10. Amanullah A, Upadhyay A, Dhiman R, Singh S, Kumar A, Ahirwar DK, et al. Development and Challenges of Diclofenac-Based Novel Therapeutics: Targeting Cancer and Complex Diseases. Cancers [Internet], Sep. 9, 2022; 14(18): 4385.
11. Sengupta S, Banerjee S, Sinha B, Mukherjee B. Improved skin penetration using in situ nanoparticulate diclofenac diethylamine in hydrogel systems: in vitro and in vivo studies. AAPS PharmSciTech [Internet], Jun. 18, 2015; 17(2): 307–17.
12. Esteruelas G, Souto EB, Espina M, García ML, Świtalska M, Wietrzyk J, et al. Diclofenac-loaded biodegradable nanoparticles as antitumoral and antiangiogenic therapy. Pharmaceutics [Internet], Dec. 28, 2022; 15(1): 102.
13. Nadalin P, Kim JK, Park SU. Recent insights into luteolin and its biological and pharmacological activities. PubMed [Internet], Mar. 12, 2024; 23: 787–94.
14. Wikipedia contributors. Luteolin [Internet]. Wikipedia, 2025.
15. Jayawickreme DK, Ekwosi C, Anand A, Andres-Mach M, Wlaź P, Socała K. Luteolin for neurodegenerative diseases: a review. Pharmacological Reports [Internet], Jun. 21, 2024; 76(4): 644–64.
16. Han Y, Xiao Y, Yu L, Chen J, Yang X, Cui H, et al. Advances in the Mechanism of Luteolin against Hepatocellular Carcinoma Based on Bioinformatics and Network Pharmacology. Journal of Cancer [Internet], Jan. 1, 2023; 14(6): 966–80.
17. Crupi R, Impellizzeri D, Bruschetta G, Cordaro M, Paterniti I, Siracusa R, et al. Co-Ultramicronized Palmitoylethanolamide/Luteolin Promotes Neuronal Regeneration after Spinal Cord Injury. Frontiers in Pharmacology [Internet], Mar. 8, 2016; 7: 47.
18. Zhang Y, Luo C, Huang P, Cheng Y, Ma Y, Gao J, et al. Luteolin alleviates muscle atrophy, mitochondrial dysfunction, and abnormal FNDC5 expression in high-fat diet-induced obese rats and palmitic acid-treated C2C12 myotubes. The Journal of Nutritional Biochemistry [Internet], Oct. 11, 2024; 135: 109780.
19. Patel R. US11844778B2 - Luteolin for treatment of neuromuscular movement disorder - Google Patents [Internet]. 2021.
20. Taheri Y, Sharifi-Rad J, Antika G, Yılmaz YB, Tumer TB, Abuhamdah S, et al. Paving Luteolin Therapeutic potentialities and Agro-Food-Pharma applications: Emphasis on in vivo pharmacological effects and bioavailability traits. Oxidative Medicine and Cellular Longevity [Internet], Jan. 1, 2021; 2021(1): 1987588.
21. Burghes AHM, Beattie CE. Spinal muscular atrophy: why do low levels of survival motor neuron protein make motor neurons sick? Nature Reviews Neuroscience [Internet], Jul. 8, 2009; 10(8): 597–609.
22. Prior TW, Swoboda KJ, Scott HD, Hejmanowski AQ. Homozygous SMN1 deletions in unaffected family members and modification of the phenotype by SMN2. American Journal of Medical Genetics Part A [Internet], Aug. 24, 2004; 130A(3): 307–10.
23. Gallotta I, Mazzarella N, Donato A, Esposito A, Chaplin JC, Castro S, et al. Neuron-specific knockdown of SMN1 causes neuron degeneration and death through an apoptotic mechanism. Human Molecular Genetics [Internet], Jun 3, 2016; 25(12): ddw119.
24. McGovern VL, Iyer CC, Arnold WD, Gombash SE, Zaworski PG, Blatnik AJ, et al. SMN expression is required in motor neurons to rescue electrophysiological deficits in the SMNΔ7 mouse model of SMA. Human Molecular Genetics [Internet], Jul. 23, 2015; 24(19): 5524–41.
25. Vashist A, Kaushik A, Vashist A, Bala J, Nikkhah-Moshaie R, Sagar V, et al. Nanogels as potential drug nanocarriers for CNS drug delivery. Drug Discovery Today [Internet], May 20, 2018; 23(7): 1436–43.
26. Brianna, Ayaz Anwar, Sin-Yeang Teow, Yuan Seng Wu, Nanogel-based drug delivery system as a treatment modality for diverse diseases: Are we there yet?, Journal of Drug Delivery Science and Technology, 2024; 91: 105224, ISSN 1773-2247.
27. Review of Nanoparticle-Based drug delivery methods in conjunction with AntiSense oligonucleotide for the treatment of spinal muscular atrophy | Research Archive of Rising Scholars [Internet].
28. Wang P, Chen Z, Li P, Mamun AA, Ning S, Zhang J, et al. Multi-targeted nanogel drug delivery system alleviates neuroinflammation and promotes spinal cord injury repair. Materials Today Bio [Internet], Jan. 23, 2025; 31: 101518.