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H-Index

4

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Citations

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Accreditations

Search..



1

2

3

4

5



Page 1 of 25 | Total Records : 244

Publications

Citation

Single step preparation of quaternary $\text{Cu}_2\text{ZnSnSe}_4$ thin films by RF magnetron sputtering from binary chalcogenide targets

RA Wibowo, WS Kim, ES Lee, B Munir, KH Kim

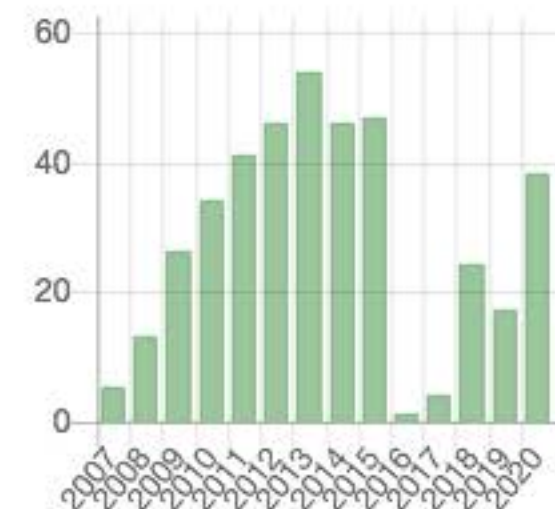
Journal of Physics and Chemistry of Solids 68 (10), 1908-1913

195

Pulsed laser deposition of quaternary $\text{Cu}_2\text{ZnSnSe}_4$ thin films

166

Citation Statistics



[ABOUT](#)[USER HOME](#)[SEARCH](#)[CURRENT](#)[ARCHIVES](#)[ANNOUNCEMENTS](#)[SITE MAP](#)[CONTACT](#) [Home](#) > Vol 7, No 1 (2021)

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Vol 7, No 1 (2021)

January

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01>

Table of Contents

Research Article

RELATIONSHIP BETWEEN LEVEL OF EDUCATION AND POST-STROKE COGNITIVE STATUS IN HOSPITAL-BASED ISCHEMIC STROKE SURVIVORS

Herpan Syafii Harahap, Yanna Indrayana, Setyawati Asih Putri

MNJ, Vol 7, No 1 (2021), pp. 1-6

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.1>

[Abstract](#) | [References](#) | [Current](#) | [PDF](#) | [Cover Page](#)

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CRANIAL ULTRASOUND: EFFICIENT SCREENING TOOL FOR EARLY DETECTION OF BRAIN INJURY IN PRETERM INFANTS

 **Dini Rachma Erawati, Yuyun Yueniwati**


 MNJ, Vol 7, No 1 (2021), pp. 7-11

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.2>

[Abstract](#) | [References](#) | [Current](#) |  [PDF](#) | [Cover Page](#)

Viewed : 0 times

DEMENTIA IN DR. SOETOMO GENERAL HOSPITAL SURABAYA: A SYNTHETIC REVIEW OF ITS CHARACTERISTICS

 **Nabilah Hasna Imami, Yudha Haryono, Anggraini Dwi Sensusiati, Muhammad Hamdan, Hanik Badriyah Hidayati**

 MNJ, Vol 7, No 1 (2021), pp. 12-16

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.3>

[Abstract](#) | [References](#) | [Current](#) |  [PDF](#) | [Cover Page](#)

Viewed : 0 times

NUMERIC RATING SCALE ANALYSIS OF TRIGEMINAL NEURALGIA PATIENTS BEFORE AND AFTER MICROVASCULAR DECOMPRESSION

 **Elena Ghentilis Fitri Amelia, Agus Turchan, Nancy Margarita Rehatta, Hanik Badriyah Hidayati**


 MNJ, Vol 7, No 1 (2021), pp. 17-19

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.4>

[Abstract](#) | [References](#) | [Current](#) |  [PDF](#) | [Cover Page](#)

Viewed : 0 times

VERTEBROBASILAR BLOOD FLOW IN GERIATRIC PATIENTS WITH HIP FRACTURES

 **Ekrem Aydın**

 MNJ, Vol 7, No 1 (2021), pp. 20-23

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.5>

[Abstract](#) | [References](#) | [Current](#) |  [PDF](#) | [Cover Page](#)

Viewed : 0 times

COGNITIVE IMPAIRMENT DETECTION IN ADULT THALASSEMIA PATIENT USING MOCA-INA

 **Chandra Calista Wardoyo, Uni Gamayani, Anam Ong, Ahmad Rizal, Yusuf Wibisono, Lisda Amalia, Ramdan Panigoro**

 MNJ, Vol 7, No 1 (2021), pp. 24-29

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.6>

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COMPARISON OF VARIOUS EEG ELECTRODE PLACEMENT SYSTEMS TO DETECT EPILEPTIFORM ABNORMALITIES IN INFANTS

Sajeesh Parameswaran, Thankappakurup Vijayamma Anil Kumar, Ajith Mohan¹, John Thomas, Nikhil Sajeed, Kamala Swarnam, Ananthanarayana Marthanda Pillai

MNJ, Vol 7, No 1 (2021), pp. 30-33

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.7>

[Abstract](#) | [References](#) | [Current](#) | [PDF](#) | [Cover Page](#)

Viewed : 0 times

THE CIDR1 α -PfEMP1 SEQUENCE FROM INDONESIAN PLASMODIUM FALCIPARUM AND ITS POTENTIAL ASSOCIATION WITH THE CEREBRAL OUTCOME

Erma Sulistyaningsih, Yunita Armiyanti, Rosita Dewi

MNJ, Vol 7, No 1 (2021), pp. 34-39

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.8>

[Abstract](#) | [References](#) | [Current](#) | [PDF](#) | [Cover Page](#)

Viewed : 0 times

Review

POTENTIAL OF ANTHOCYANIN BASED POLY (METHYL METHACRYLATE) NANOPARTICLES SPECIFIC ACTIVATED MICROGLIA IN MANAGEMENT INFLAMMATORY PAIN ON HERNIATED NUCLEUS PULPOSUS: A LITERATURE REVIEW

I Putu Eka Widyadharma, Agung Bagus Sista Satyarsa, Feliani Sanjaya, Ni Made Gitari, I Wayan Nirvana, Thomas Eko Purwata, I Made Jawi, Dewa Ngurah Suprpta, AA Raka Sudewi

MNJ, Vol 7, No 1 (2021), pp. 40-47

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.9>

[Abstract](#) | [References](#) | [Current](#) | [PDF](#) | [Cover Page](#)

Viewed : 0 times

EFFICACY AND SAFETY OF DULOXETINE IN THE TREATMENT OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY: A SYSTEMATIC REVIEW AND META-ANALYSIS

I Putu Eka Widyadharma, Chiquita Putri Vania Rau, Rizaldy Taslim Pinzon, Yudiyanita Y, Agung Wiwiek Indrayani, Thomas Eko Purwata, Boya Nugraha

MNJ, Vol 7, No 1 (2021), pp. 48-55

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.10>

Visitor Statistic

US	41983	ID	19884
CA	18103	VN	15659
RU	11647	DE	8980
IN	8850	FR	6953
BR	6443	IT	5707

Newest: BZ You: ID

Today: 43

Month: 649

Total: 227804

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Index


DOAJ
DIRECTORY OF
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JOURNALS

INDEX
COPERNICUS
INTERNATIONAL

Crossref

Google

EFFECTIVITY OF NINTENDO WII AS REHABILITATION THERAPY IN POST STROKE PATIENTS: A SYSTEMATIC REVIEW

 **Rachmawati Wardani, Sirin Salsabila, Arizal Novrianto Rahman, Rodhiyan Rakhmatiar**


 MNJ, Vol 7, No 1 (2021), pp. 56-59

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.11>

[Abstract](#) | [References](#) | [Current](#) |  **PDF** | [Cover Page](#)

Viewed : 0 times

SEIZURES IN CHILDREN WITH LOW GRADE GLIOMA

 **Piyush Ostwal, Shanbhag Nandan**

 MNJ, Vol 7, No 1 (2021), pp. 60-65


DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.12>

[Abstract](#) | [References](#) | [Current](#) |  **PDF** | [Cover Page](#)

Viewed : 0 times

Case Report

A CASE REPORT OF ACUTE NONTRAUMATIC SPONTANEOUS SUBDURAL HAEMATOMA DUE TO PSEUDOANEURYSM OF MIDDLE MENINGEAL ARTERY

 **Feda Makkiyah, Rahma Nida Nurrahmah**

 MNJ, Vol 7, No 1 (2021), pp. 66-69

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.13>

[Abstract](#) | [References](#) | [Current](#) |  **PDF** | [Cover Page](#)

Viewed : 0 times

THE DAMAGE OF THE OPTIC NERVE AS THE OUTCOME OF UNINTENTIONAL POISONING BY CLOSANTEL

 **Evgenia Sergeevna Kurakina, Elena Eduardovna Ioyleva, Mutlaq Ali Saif Saif, Natalia Alexandrovna Gavrilova**

 MNJ, Vol 7, No 1 (2021), pp. 70-73

DOI: <http://dx.doi.org/10.21776/ub.mnj.2021.007.01.14>

[Abstract](#) | [References](#) | [Current](#) |  **PDF** | [Cover Page](#)

Viewed : 0 times

HEMICHOREA-HEMIBALLISM IN VARIOUS CONDITIONS: SERIAL CASE REPORTS

 **Neila Raisa, Sri Budhi Rianawati, Shahdevi Nandar Kurniawan, Fahimma F, Mulika Ade Fitria Nikmahtustsani**

 MNJ, Vol 7, No 1 (2021), pp. 74-79



Journal Content

Search

Search Scope

All



[ABOUT](#)[USER HOME](#)[SEARCH](#)[CURRENT](#)[ARCHIVES](#)[ANNOUNCEMENTS](#)[SITE MAP](#)[CONTACT](#) [Search](#)[Home](#) > [Vol 7, No 1 \(2021\)](#) > [Widyadharma](#)

POTENTIAL OF ANTHOCYANIN BASED POLY (METHYL METHACRYLATE) NANOPARTICLES SPECIFIC ACTIVATED MICROGLIA IN MANAGEMENT INFLAMMATORY PAIN ON HERNIATED NUCLEUS PULPOSUS: A LITERATURE REVIEW

I Putu Eka Widyadharma, Agung Bagus Sista Satyarsa, Feliani Sanjaya, Ni Made Gitari, I Wayan Nirvana, Thomas Eko Purwata, I Made Jawi, Dewa Ngurah Suprpta, AA Raka Sudewi

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Abstract

Pain is an unpleasant sensory and emotional experience that can affect the quality of life and leads to decreased productivity in patients. Low back pain (LBP) is one of the significant causes of disability worldwide with lifelong incidence. The purpose of this literature review describes the potential of anthocyanin-based Poly (Methyl Methacrylate) (PMMA) nanoparticles as the management of inflammatory pain in the Hernia Nucleus Pulposus (HNP). The method used is a literature study by entering the keyword. Of the 77 journals reviewed, 47 journals were found by the topic and used as a reference for this work. The

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anthocyanin-based PMMA nanoparticles act as anti-nociceptors by inhibiting microglia that produce inflammatory mediators in HNP. Poly (Methyl Methacrylate) nanoparticles have specific targets in microglia. Anthocyanins have the effect of inhibiting inflammatory pain through many destinations. Anthocyanin inhibits the synthesis of nitric oxide (NO) and prostaglandin E2 (PGE 2) and inhibits the activation of p38 MAPK and NF-kB pathways that express TNF- α and IL-1 β genes as anti-nociceptive. The anthocyanin-based PMMA nanoparticles have potential as a novel therapy for inflammatory pain in HNP. There has been no research between these modalities. Therefore, further research is needed to find out the exact potential of anthocyanin-based PMMA nanoparticles.

Keywords

Anti-nociceptive; Anthocyanin; Hernia Nucleus Pulposus; and Poly (Methyl Methacrylate) Nanoparticles

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References

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ABSTRACT

Pain is an unpleasant sensory and emotional experience that can affect the quality of life and leads to decreased productivity in patients. Low back pain (LBP) is one of the significant causes of disability worldwide with lifelong incidence. The purpose of this literature review describes the potential of anthocyanin-based Poly (Methyl Methacrylate) (PMMA) nanoparticles as the management of inflammatory pain in the Hernia Nucleus Pulposus (HNP). The method used is a literature study by entering the keyword. Of the 77 journals reviewed, 47 journals were found by the topic and used as a reference for this work. The anthocyanin-based PMMA nanoparticles act as anti-nociceptors by inhibiting microglia that produce inflammatory mediators in HNP. Poly (Methyl Methacrylate) nanoparticles have specific targets in microglia. Anthocyanins have the effect of inhibiting inflammatory pain through many destinations. Anthocyanin inhibits the synthesis of nitric oxide (NO) and prostaglandin E2 (PGE2) and inhibits the activation of p38 MAPK and NF-κB pathways that express TNF-α and IL-1β genes as anti-nociceptive. The anthocyanin-based PMMA nanoparticles have potential as a novel therapy for inflammatory pain in HNP. There has been no research between these modalities. Therefore, further research is needed to find out the exact potential of anthocyanin-based PMMA nanoparticles.

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Introduction

Pain is an unpleasant sensory and emotional experience that can affect the quality of life and cause a decrease in productivity.^{1,2} LBP is one of the leading causes of disability worldwide with a lifetime of around 51 % - 84% and more than 10% of people at all times.³ The incidence of LBP in some developing countries is approximately 15% - 20% of the total population and 40% of LBP cases are caused by Hernia Nucleus Pulposus (HNP).¹

About 95% of intervertebral hernias occur in L4-L5, or L5-S1.^{2,4} Hernias can be caused by age, genetic, or environmental factors such as smoking and strenuous activity.⁴ The clinical manifestation of HNP is ischialgia or sharp pain such as burning and pulsing to the bottom of the knee and usually most often appears on the posterolateral aspect of the intervertebral disc.^{2,4}

HNP is a condition in which part or all of the nucleus pulposus experiences protrusion into the spinal canal, but the shrinking nucleus pulposus will distribute the load asymmetrically so that it can cause injury or tear in the annulus.² Contact from the nucleus pulposus with nerve roots will trigger inflammation resulting in pain.^{4,5} Radicular lumbar pain due to HNP causes significant morbidity.⁵ Glial cells, especially astrocytes and microglia, are known to be essential modulators in nociceptive.⁶ Glia cells can interact directly with neurons and play a crucial role as neuromodulators and neuroprotection of the central nervous system (CNS).⁷ Spinal cord is an area where microglia density is very high. The number of microglia will increase dramatically after an injury to the peripheral nerves.⁸ Microglia becomes easily active in response to injury, infection, or inflammation and is able to produce various pro-inflammatory mediators such as nitric oxide (NO), prostaglandin E2 (PGE2), reactive oxygen species

(ROS), interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and tumor necrotic factor- α (TNF- α), as well as other potentially neurotoxic compounds.^{9,10} Glial activity in CNS and inflammation after nerve injury will result in hyperalgesia and allodynia.¹¹

Microglia play an essential role in the development of pain, so microglia and related signaling molecules are promising targets for pain control. The benefits of microglia molecule targeting therapy are fewer side effects because most of these molecules will be regulated mainly in microglia activation.¹²

At present, the management of pain in HNP is carried out by medical rehabilitation programs, surgery in severe cases or in pain that is strongly associated with the activity, and with analytical drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants and muscle relaxants.² The effectiveness of using analgesics, antidepressants, or relaxants in patients with hernias have not been proven.¹³ Acetaminophen can reduce back in the short term, but the benefits are unclear and ineffective in patients with sciatica. In a randomized trial, therapy with systemic glucocorticoids was found to improve physical function, but could not reduce significant pressure and reduce subsequent surgery.⁴ Steroids can overcome several inflammatory cytokines and chemokines. Caudal epidural (CESI) steroid injections can be used for the treatment of radicular lumbar pain, but in clinical practice, many patients who deal with it in this way remain persistent neuropathic support.¹¹

Besides, epidural injections can be useful in 80% of cases, but patients need fourth to fifth injections in one year, and steroids can be released from natural resorption of the nucleus pulposus (NP) tissue extruded.¹⁴ At present, the anticonvulsants of gabapentin have wide acceptance as a standard drug for neuropathic pain including trauma to nerve injury pain.¹⁵ However, the use of gabapentin can cause side effects such as sedation, dry mouth, constipation, regulating, pushing and peripheral edema. In some patients, mostly in the elderly, the use of gabapentin and amitriptyline prevents because it can cause or worsen cognitive impairment.¹⁶

Surgical treatment (discectomy) cannot restore the normal function of the intervertebral disc, and the rate of recurrence of surgery in disc hernia patients is around 18%, even 15% require repeat surgery because it is increasing.^{17,18} Therefore, a more effective modality for use is needed to overcome problems caused by HNP without causing a slowdown in the natural resorption of NP tissue.

Many benefits have been developed from plant phenolic compounds such as antioxidants, anti-inflammatory, anti-viral and anti-carcinogenic. Some flavonoids isolated from plants were found to have a significant effect as anti-nociceptive (analgesic) and anti-inflammatory effects.¹⁹ Anthocyanin can offer substantial potential therapy to treat inflammatory and neurodegenerative diseases that require microglia approval by inhibiting pro-inflammatory mediators.¹⁵ In the studio, it was found that anthocyanin significantly stopped pro-inflammatory mediators without cytotoxicity difficulties and could increase ROS production.^{19,20}

Based on various studies, it has been shown that polymeric nanoparticles or poly (methyl methacrylate) nanoparticles (PMMA-NPs) have the potential to treat spinal cord injury (SCI) and can be a specific therapy for microglia targets. The modality of PMMA-NPs has been tested for validity, which can be a good conductor with a short period of treatment and fast half-life without any side effects on the body. According to the study of Papa²⁰ et al., it was stated that PMMA-NPs have significant potential as an anti-inflammatory therapy with specific targets of microglia in SCI. In addition, PMMA-NPs can act as precise drug delivery to microglia as indicated by macrophage inhibition by mimetic drugs (To-Pro3).²⁰ Based on the exposure of the data and facts above, active anthocyanin-based PMMA nanoparticles can be a novel therapeutic modality by maximizing anthocyanin potential as management of pain in future HNPs.

Methods

The writing of this scientific literature review uses a literature study method based on the results of studies of various literature that have validity tested, relate to each other, and support the discussion or analysis of the discussion. The literature review uses the database www.pubmed.com and www.scholar.google.com using keywords: "Anti-nociceptive, Anthocyanin, Nucleus Pulposus Hernia (HNP), and Poly Nanoparticles (Methyl Methacrylate) (PPMA)." The library study method is only intended for scientific journals that use English, Indonesian, and have abstracts in these scientific journals. Titles and abstracts will undergo a scanning process to exclude scientific journals that are irrelevant to HNP, Anthocyanin's, PMMA nanoparticles and anti-nociceptive. Scientific journals that have successfully passed the inclusion and exclusion criteria will undergo the scanning process again to find out additional publications regarding HNP, anthocyanin, PMMA-NPs, and anti-nociceptive.

In this literature review, we use all scientific journals that discuss the analysis of benefits, working mechanisms, and the clinical effects of PMMA nanoparticles with anthocyanin as management of inflammatory pain in HNP. A scientific journal will undergo an exclusion process if the publication year or year of publication of the journal has exceeded ten years. There are 77 scientific articles or journals by the topics discussed, but only 47 journals or publications that meet the inclusion and exclusion criteria set by the author.

Discussion

Pathogenesis of Inflammatory Pain in HNP

Pain in HNP is caused by a pathological process in the vertebral column in the intervertebral disc.²¹ Looks like a lumbar disc hernia such as lower back and sciatica associated with the release of local cytokines followed by an induced inflammatory process using NP contacts with the spinal cord. Prolonged contact with NP with dorsal root ganglia (DRG) is increasingly increasing because it increases chronic complications.^{11,22,23}

The structure of NP consists of proteoglycans, collagen, and supporting cells that are capable of producing

inflammatory mediators after defense. During the inflammatory process, nociceptive neurons become sensitized and begin to respond to a stimulus that has not received a prior response; this is called hyperalgesia. Hyperalgesia is a common denominator of all inflammatory processes and is characterized by a decrease in threshold and increased activity in thermal and mechanical stimulus stimuli. This hyperalgesia stage can improve the response to mechanical, thermal and chemical stimulation and improve synaptic conduction efficiency.²³

After nerve injury, the inflammatory mediator is released from the primary afferent terminal to the spinal cord, and there is cell transfer based on microglia and astrocytes in the spinal horn of the back by several inflammatory molecules. Glial activation leads to a pro-inflammatory response with pathological effects, such as neuronal hyperexcitability, chronic neurotoxicity, and inflammation, which improves neuropathic healing.²⁴ Abnormal activation of microglia produces a primary cellular response that plays an essential role in the pathogenesis of the inflammatory response.^{15,18}

Specific cytokines released during the inflammatory process play an important role in the development of two modalities of hyperalgesia (thermal and mechanical), so that maintenance of inflammation plays an important role in chronic healing. The release of cytokines such as IL-1, IL-6, IL-8, TNF α , and PGE2 is related to radicular healing in nerve root damage due to HNP.^{11,14,22,23}

Role of Microglia: Response to Pathogenesis of Pain in HNP

Neuroglia cells such as astrocytes and microglia in the spinal cord will become active after nerve damage and inflammation in the DRG. Chemical release mediators cause sensitization of the sensory nerves and the formation of neuromas that cause ectopic activity. Inhibition of neurons inhibits degeneration caused by increased afferent input and microglia activation.²⁵

HNP also results in ATP release, resulting in P2X4 and P2X7 receptor activation in microglia.²⁶⁻²⁸ P2X4 receptor activation in microglia facilitates Brain-derived neurotrophic factor BDNF, while P2X7 receptor activation in microglia induces a release of IL-1 β and production CXCL2.^{17,29,30} Peripheral nerve injury leads to increased regulation of P2X4 receptors in activated microglia. ATP acting on P2X4 receptors in microglia will induce an increase in intracellular Ca²⁺ and phosphorylation of p38, which then increases the synthesis and release of BDNF. BDNF release from microglia can produce a depolarization shift in the potential for Cl⁻-reversal by decreasing the expression of exporters of potassium chloride KCC2 in the dorsal horn neuron thereby facilitating mechanical allodynia after nerve injury.¹²

Based on the study of Zhuo¹² et al., There was activation of p38 which resulted in transcription of the NF- κ B factor, leading to the expression of IL-1 β , IL6, and cyclooxygenase-2 (COX-2). Cytokines released by activated microglia will amplify microglia activation autocrine and can act directly on the dorsal horn neurons causing sensitization of pain.¹²

Based on the results of previous studies, it was shown that after nerve injury there would be activation of microglia

receptors. Nerve injury results in spontaneous activity that causes the release of chemokines (e.g., MCP-1) from primary sensory DRG neurons. MCP-1 activates the CCR2 receptor in microglia. Spontaneous activity can also release proteinase, causing division of fractal chemokine (FKN). FKN will bind CX3CR1 to microglia, causing the production of cytokines namely TNF α and IL-1 β .²⁷

The Mechanism of Construction of Anthocyanin-Based PMMA Nanoparticles

Anthocyanin compounds can be found in several plants, especially seen in purple yams/sweet potato (*Ipomoea batatas* L).³¹⁻³³ anthocyanins are known as flavonoids but are distinguished from flavonoids because they can form flavylium cations.^{34,35} Anthocyanin compounds consist of carbon frames with hydrogen, hydroxyl, and methoxyl groups found in six different positions. The anthocyanin pigment includes an aglycone (anthocyanidin) which is esterified by one or more glucose.³⁶

A study conducted at Udayana University found the anthocyanin content in 100 grams of purple sweet potato processed by powder formation extraction ranges from 110 mg to 210 mg.³⁷ Anthocyanin in purple sweet potato is found in the form of a mono or diacylated cyanidin and peonidin which have high antioxidant activity.^{39,40} The color density of purple sweet potato correlates with its anthocyanin content, the more purple the tuber, the higher the anthocyanin content it contains. The anthocyanin content in purple sweet potato can reach 508.45-645.37 ppm.³⁴

PMMA-NPs are reduced into polymerization piles with free radicals (BEP) using KPS or 2,2-Azobis (2-methylpropionamide). The reaction was carried out using 100 mL of three fluted neck glass equipped with a reflux condenser. Temperature is controlled with an external bath oil set to 80 \pm 1 $^{\circ}$ C. After that, for the BEP reaction, 2.5 g PMMA, which is measured by the HEMA-RhB macro-monomer. The system is cleaned with syringes. This system is maintained under a magnetic stirrer at 350 rpm. Finally, 0.04 g of the right initiator is added to start the reaction. The reaction is carried out for 3 hours; the conversion economimer has been measured by gravimetric measurements and calculated as higher than 99.5%. After synthesis, the pH is adjusted using 0.1 M NaOH until pH reaches 7. The result is latex with a size of 5% w / w. Then, the size and polydispersity of the NP suspension index were collected from Dynamic Light Scattering (DLS). After that, measurements were taken (Malvern, Zeta Nano ZS), and the data reported was the average value of the same two sample measurements.⁴⁰

Anthocyanin can be combined with PMMA-NPs using polymerization reaction. First, the PMMA-NPs 1 ml latex concentration of latex PMMA-NPs at 25% b / b was obtained in the presence of aggregates by DLS measurements. Concentrated latex was incubated with 20 μ g for 100 μ g anthocyanin, in one day at room temperature with gentle magnetic stirring. Then centrifuged at 4000 rpm for 15 minutes. The result is stable anthocyanin-based PMMA nanoparticles and is ready to be used orally.

Potential of HNP Pain Relief: Anthocyanin Based PMMA Nanoparticles

Based on the results of the study of Papa²⁰ et al., It stated that PMMA-NPs could be administered orally. The modalities of PMMA nanoparticles with 100% bio-viability with specific microglia mark on DRG. PMMA-NPs bind to LPS-microglia. Furthermore, endocytosis of the nanoparticles will occur, which causes anthocyanin to be active in microglia. Anthocyanin activation will inhibit pro-inflammatory mediator production, TNF α , and IL-1 β , which inhibit PGE2 so that it can reduce pain response.

Glial cells have close interactions with neurons in modulating pain transmission, especially in pathological conditions. Activation of spinal glia after nerve injury is known to cause the production and release of pro-inflammatory cytokines that can affect hyper-sensitivity from the spinal cord, thus inhibiting pro-inflammatory mediators and cytokines will be an effective therapeutic approach to reduce the development of neurodegenerative and painful diseases.¹⁵

Based on various studies that have been done, anthocyanin is known to have antioxidant, anti-inflammatory, antimicrobial and anti-carcinogenic activities, improve visuals, induce apoptosis and neuroprotective effects and can prevent degenerative diseases such as atherosclerosis.^{34,35,41} Based on the study results of Jeong¹⁹ et al., anthocyanin can inhibit pro-inflammatory mediators by reducing NO and PGE2 synthesis, each of which is a product of iNOS-induced isoforms and COX-2 enzymes. In vitro studies have shown that anthocyanin significantly suppresses the expression of iNOS and COX-2 so that it can suppress NO and PGE2 production. The effect of anthocyanin depends on its concentration; the anthocyanin concentration of 100 $\mu\text{g} / \text{mL}$ can reduce NO production to > 72% so that the production of PGE2 can be inhibited by 98%.¹⁹ Based on the study results of Jeong et al., anthocyanin can inhibit pro-inflammatory mediators by reducing NO and PGE2 synthesis, each of which is a product of iNOS-induced isoforms and COX-2 enzymes. In vitro studies have shown that anthocyanin significantly suppresses the expression of iNOS and COX-2 so that it can suppress NO and PGE2 production. The effect of anthocyanin depends on its concentration; the anthocyanin concentration of 100 $\mu\text{g} / \text{mL}$ can reduce NO production to > 72% so that the production of PGE2 can be inhibited by 98%.¹⁹ Other pro-inflammatory cytokines produced by microglia activated during inflammation are TNF- α and IL-1 β . In an additional, study from Jeong¹⁹ et al., that anthocyanin can modulate TNF- α and IL-1 β gene expression. Anthocyanin inhibits TNF- α and IL-1 β gene expression at the transcription level which results in reduced production of TNF- α and IL-1 β . So that it can suppress the formation of prostaglandin as a pain response.

Based on previous studies, it has also been shown that anthocyanin affects the regulation of NF-kB which occurs anti-inflammatory.¹⁵⁻²¹ NF-kB can induce transcription of the pro-inflammatory gene, which is influenced by binding of NF-kB to a specific promoter region. NF-kB is usually located in the cytoplasm with the inhibitory complex of I κ B. In response to pro-inflammatory stimuli, I κ B will be phosphorylated and then degraded, NF-kB will be released and translocated to the nucleus to produce expression of inflammatory-related genes.^{19,20}

Evidenced from the results on Jeong¹⁹ et al., That anthocyanin's significantly reduced the release of pro-inflammatory mediators and cytokines by blocking NF-kB pathway, the cells of LPS-induced microglia BV without causing cytotoxicity. Anthocyanin inhibits pro-inflammatory gene expression by suppressing LPS inducing NF-kB activity and significantly inhibiting Akt activation in BV2 microglia cells stimulated by LPS.

Besides, the MAPK pathway is also known to be involved in activating pro-inflammatory transcription factors; NF-kB and AP-1.⁴³ Recent research shows that the Akt signal molecule triggers NF-kB activation through I κ B degradation. In the study of Jeong et al., It was found that anthocyanin was able to inhibit phosphorylation of Akt and MAPKs in BV2 microglia cells stimulated by LPS.²⁰ This shows that anthocyanin can have a beneficial effect of treating inflammation and neurodegenerative damage caused by microglia activation. But further research is needed regarding the anti-inflammatory effects of anthocyanin's in vivo.¹⁹

In addition, ROS such as hydrogen peroxide (H₂O₂) and superoxide (O₂⁻) are thought to play an important role in sensitization during persistent pain. Antioxidants can protect the body against ROS so that it can be useful to prevent intervertebral disc degeneration. Studies in vitro and in vivo show that cyanidin chloride and cyanidin glucoside have effects in inhibiting ROS. Anthocyanin can enhance the clearance of superoxide radicals and inhibit oxidative damage. Anthocyanin cyanidin 3-O-glucoside is effective in inhibiting ROS production both due to stimulation of LPS and IFN- γ . Cyanidin 3-O-glucoside was stronger in inhibiting ROS production due to IFN- γ stimulation, by showing a significant reduction of more than 80% in 6.25pMS.^{33,43,44}

Glial cells in the dorsal horn spine such as microglia and astrocytes, are activated in response to stimulation due to nerve injury and peripheral tissue injury and are involved in nociceptive transmission and central sensitization. Glial activation is directly involved in inflammatory and neuropathic pain. A number of mechanisms are believed to play a role for induction and maintenance of glia-related persistent pain, namely activation of mitogen-activated protein kinase (MAPKs), such as extracellular signal-regulated kinase (ERKs), p38 MAPK and c-Jun N terminal kinase (JNK), regulated by P2 purinoceptors, and increases in pro-inflammatory cytokines such as IL-1 β , IL-6, TNF- α and IL-18, and chemokines such as CCL2.⁴⁴

Advantages of Anthocyanin based PMMANs as Management of Chronic Pain in HNP

PMMA nanoparticles have specific microglia targets that are promising pain therapy modalities. Besides, PMMA-based nanoparticles do not show significant toxic effects because they do not alter the main biological features such as bioavailability, cell growth, and metabolic activity so that there is a substantial potential for delivering drugs.^{45,46}

Anthocyanins inhibit pain by a multi-target mechanism and can inhibit the synthesis of pro-inflammatory mediators in NP without causing natural resorption of NP extrusion tissue, making it a practical approach to treat pain due to HNP. Also, the antioxidant effects of anthocyanin's can also

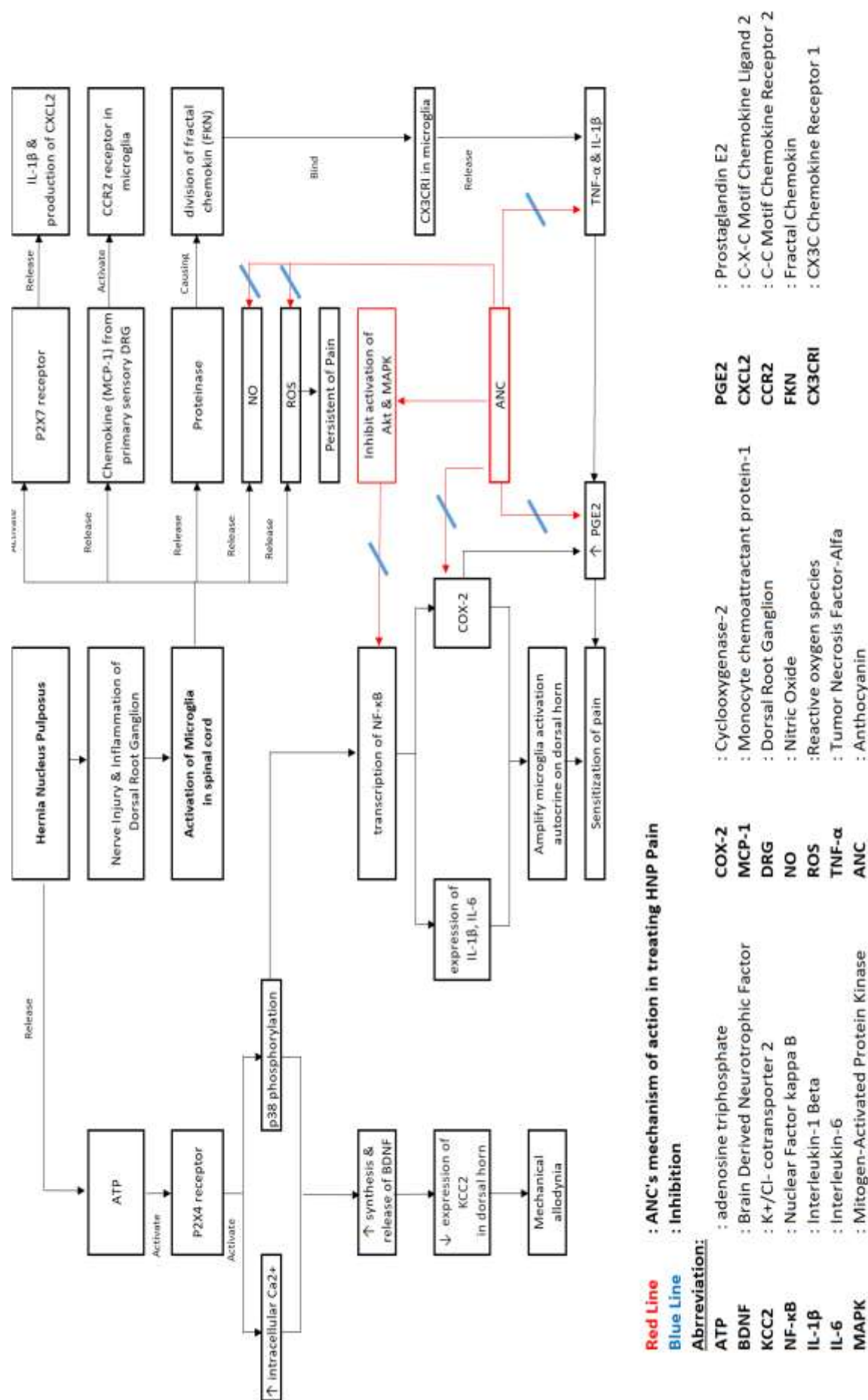


Figure 1. Role of Anthocyanin in HNP Pain Management

play an essential role in preventing degeneration and protecting the intervertebral discs against ROS.¹⁹

This modesty, not only can be used in pain due to NP but can also be used in the management of pain whose pathophysiology is based on inflammation. This anthocyanin potential also has advantages as natural ingredients and phytopharmaca from purple sweet potatoes which are commonly found on the Indonesian mainland.

The maximum utilization of bioactivity from anthocyanins can increase the potential of nature and biological wealth in Indonesia. The pathophysiology of pain in HNP and the role of anthocyanin in the management of pain in HNP can be seen in Figure 1.

The Limitations of Anthocyanin-based PMMANs as HNP Pain Management

The limitations of anthocyanin-based PMMA nanoparticles namely PMMANs are suitable as carriers of antioxidant compounds, but there are no studies that address the relationship of anthocyanin-based PMMA nanoparticles. Also, anthocyanin is a flavillium derivative compound and fundamentally lacks electrons, so it is reactive to changes in pH and temperature, this causes anthocyanin stability to be affected by changes in temperature and pH.⁴⁸

Conclusion

Based on the results of the literature review, anthocyanin-based PMMA-NPs have the potential to be applied as a therapy for pain management in HNP. It can also be seen from the superiority of specific PMMA nanoparticles targeting microglia. Also, anthocyanin-based PMMA nanoparticles are easily obtained and have no side effects and toxic effects as pain management in HNP. It is expected that anthocyanin-based PMMA-NPs can reduce the pain response in HNP. Thus, anthocyanin-based PMMA nanoparticles can be used to manage pain in HNP in the future.

Further research is needed on a higher level regarding anthocyanin-based PMMA nanoparticles to determine the efficacy of HNP both in vitro and in vivo. It is hoped that with sufficient scientific evidence, anthocyanin-based PMMA nanoparticles can be used as management of pain in HNP in the future.

Conflicy of Interest

We declare no conflict of interest.

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