Journal for ReAttach Therapy and Developmental Diversities
eISSN: 2589-7799
2023 October; 6 (9s): 776-783

Kynurenic Acid and Acupuncture on Chronic Pain

Karina Pratiwi[1*], Nancy Margarita Rehatta[1], Ario Imandiri[2], Wiwiek Indriyani Maskoep[3], Pungky Mulawardhana[4]

[1]Department of Anesthesiology and Intensive Care, Dr. Soetomo General Hospital, Surabaya, East Java, Indonesia
[2]Faculty of Vocational Studies, Universitas Airlangga, Surabaya, East Java, Indonesia
[3]Department of Palliative and Pain-free, Dr. Soetomo General Hospital, Surabaya, East Java, Indonesia
[4]Department of Obstetrics and Gynecology, Airlangga Hospital, Surabaya, East Java, Indonesia
*Correspondence: karinapratiwi22@gmail.com

Received: 26-09-2023
Revised: 29-09-2023
Accepted: 02-10-2023
Online First: 04-10-2023

Abstract

Introduction: Approximately 20% of the population experiences chronic pain. Chronic pain is characterized as a persistent sensation of discomfort that lasts for a duration exceeding three months subsequent to the experience of a traumatic incident or inflammation. Chronic pain can present itself in either intermittent or chronic patterns, often accompanied by a parasympathetic physiological response. Chronic pain is linked to a range of adverse consequences, such as impairments in the execution of everyday activities, dependence on opioid analgesics, heightened levels of anxiety, and manifestations of depressive symptoms. The therapeutic effectiveness of tryptophan and its metabolites, including kynurenic acid, exhibits encouraging indications in the management of chronic pain. Acupuncture has been utilized as an adjunctive therapeutic modality for centuries in the management of chronic pain. Acupuncture possesses the capacity to influence individuals' perception of pain at an emotional level, inducing a tranquil emotional state and promoting heightened relaxation in patients.

Objectives: This study aims to systematically investigate the effects of acupuncture on kynurenic acid, a variable that functions as an objective measure of pain.

Methods: We conducted a literature review in the PubMed, Scopus, and Web of Science databases referring to how acupuncture and kynurenic acid contribute to reduction of chronic pain.

Results: The acupuncture interventions varied in terms of techniques, frequency, and duration. The findings revealed a consistent trend of increased kynurenic acid levels following acupuncture treatments in chronic pain patients. However, the magnitude of this increase varied among studies. Additionally, several studies reported improvements in pain severity and reduction in opioid reliance among participants receiving acupuncture. Methodological quality assessments indicated moderate to high quality among the included studies. Despite the overall positive trend, some heterogeneity was observed in the response to acupuncture across different pain conditions. These results suggest that acupuncture may hold promise as a complementary therapy for chronic pain management, with kynurenic acid serving as a potential biomarker for monitoring treatment effectiveness.

Conclusions: Acupuncture has been shown to be beneficial in relieving chronic pain, and the use of kynurenic acid can aid in the objective assessment of its efficiency.

Keywords: acupuncture, kynurenic acid, chronic pain.

1. Introduction

In conjunction with the International Association for the Study of Pain (IASP), Cohen et al. define pain as an aversive sensory and affective encounter that is linked to real or potential harm to bodily tissues or is perceived as such harm (Cohen et al., 2018; Nicholas et al., 2019). According to this concept, it is implied that factors outside

tissue damage might serve as determinants, and individuals may feel pain even in the absence of observable tissue damage.

Chronic pain (CP) is characterized by its persistence for a duration beyond three months following the occurrence of a traumatic event or inflammation. CP may exhibit intermittent or persistent patterns, often accompanied by a parasympathetic physiological response. CP is associated with various adverse effects, including restrictions in performing routine tasks, reliance on opioid medications, heightened levels of anxiety, and symptoms of depression (Sherwood, 2016). Based on current study findings, it has been determined that CP carries a greater economic burden compared to other diseases (Dahlhamer et al., 2018). Additionally, statistical data reveals that about one in every five persons experiences CP, showing a notable prevalence of this particular health condition (Yong et al., 2022). Furthermore, it should be noted that the financial burden associated with the treatment of individuals suffering from CP amounts to a range of 560 million to 635 million rupiahs annually (Waloejo et al., 2022).

Kynurenic acid (KYNA) is a byproduct derived from a specific branch of the kynurenine (KYN) pathway, which is involved in the metabolic breakdown of tryptophan (TRP). The potential therapeutic efficacy of TRP and its metabolites, such as KYNA, in the management of CP, exhibits encouraging prospects. KYNA has neuromodulatory properties, anti-inflammatory effects, and serves as an antagonist of N-methyl-D-aspartate (NMDA) receptors, hence potentially inhibiting glutamate receptor activity in animals, which reduces pain (Jovanovic et al., 2020).

Acupuncture, as a kind of complementary therapy, has been employed for centuries in the treatment of CP. A recent study found that acupuncture has the capability to impact the affective dimension of pain, inducing a state of emotional tranquillity and promoting heightened relaxation among patients (White et al., 2008). It has been shown that acupuncture can regulate TRP metabolism (Zhang et al., 2020), including KYNA (Bao et al., 2021).

2. Objectives

This paper aims to objectively examine the effects of acupuncture on KYNA, a variable that serves as an objective measure of pain, among patients suffering from a wide spectrum of CP conditions. By examining the existing body of literature, we aimed to elucidate the potential therapeutic role of acupuncture in modulating KYNA levels and its implications for pain management. This study sought to provide insights into the effectiveness of acupuncture as a complementary therapeutic intervention for diverse CP types, with a particular focus on its influence on KYNA as a potential biomarker for assessing pain severity and treatment outcomes.

3. Methods

In this study, a literature review was conducted to investigate the impact of acupuncture on KYNA in the management of CP. Data sources including PubMed, Scopus, and Web of Science were searched for relevant studies published up to the present. Inclusion criteria comprised original research articles involving human participants published in English, while exclusion criteria encompassed studies involving animals, reviews, non-relevant publications, and non-English literature. Data extraction was carried out by two independent reviewers, focusing on study design, participants, acupuncture interventions, KYNA-related outcomes, and findings. A narrative synthesis was employed to thematically summarize findings, addressing any study heterogeneity. Ethical approval was not required as this study constituted a systematic review of publicly available literature. This methodology outlines our systematic approach to exploring the relationship between acupuncture, KYNA, and CP, contributing insights to the existing knowledge.

4. Results

Chronic Pain

Acute to chronic pain appears to proceed in discrete pathophysiological and histological phases. Peripheral receptors and endogenous defense mechanisms function similarly regardless of the insult that causes a nociceptive response. Leucocytes, macrophages, chemical, mechanical, and thermal sensors determine noxious event

intensity, location, and duration. Noxious stimuli activate second-order neurons in the spinal cord's dorsal horn via amino acid and peptide transmitters. The brain receives impulses from spinal neurons. The individual uses sensory-discriminative, motivational-affective, and modulatory processes to reduce or end the pain. Normal healing reduces unpleasant stimuli and discomfort until none is felt. However, persistent, acute pain triggers peripheral and central nervous system mechanisms that generate allodynia, hyperalgesia, and hyperpathia, which can impair normal functioning. The modifications start in the peripheral with cyclo-oxygenase-2 and interleukin-1β-sensitizing first-order neurons, which then activate NMDA channels and signal microglia to change neuronal cytoarchitecture in second-order spinal neurons. Prostaglandins, endocannabinoids, ion-specific channels, and scavenger cells help change acute to CP. Understanding how these drugs interact will help create CP treatments (Voscopoulos & Lema, 2010).

Pain is categorized as nociceptive, neuropathic, or a mix of both, based on its underlying mechanism. Pain arises as a result of the stimulation of nociceptive receptors, which occurs due to injury or harm inflicted against non-neural bodily tissues, whether somatic or visceral in nature. Individuals suffering from osteoarthritis, rheumatoid arthritis, gouty arthritis, arthralgia, low back pain, and myalgia commonly feel discomfort (Haefeli & Elfering, 2006). Nevertheless, the term neuropathic pain is used to describe pain that arises from basic injury to the nervous system. The processes behind neuropathic pain can be categorized into central and peripheral pathways. Central pain is characterized by the manifestation of pain in the peripheral nervous system tissue. On the other hand, peripheral pain is observed in individuals who have undergone a stroke or post-spinal trauma.

A notable proportion of individuals diagnosed with cancer, ranging from twenty to fifty percent, encounter pain, and around 80% encounter varying degrees of pain that can be classified as moderate to severe (Bruera & Kim, 2003; Fischer et al., 2010; van den Beuken-van Everdingen et al., 2007). There is a greater vulnerability to cancer pain and broad pain in younger patients in comparison to older patients (Green & Hart-Johnson, 2010). The presence of pain among those diagnosed with cancer might elevate the susceptibility to psychological illnesses, including anxiety, sadness, and suicide ideation (Chapman, 2012). In addition to the inherent pain associated with cancer, pain experienced by individuals with cancer can also arise from the side effects of medications, surgical procedures, radiation, and chemotherapy (Chapman, 2011).

The majority of pain experienced by individuals is somatic in nature and typically manifests as either a continuous or intermittent sensation (Gutgsell et al., 2003). Cancer pain may be categorized based on pathophysiological characteristics into two main types: nociceptive pain and neuropathic pain. Nociceptive pain refers to the sensation of pain that arises from the activation of specialized sensory receptors known as nociceptors, which occur as a result of actual or potential harm to non-neural tissues. Pain can be classified as either somatic or visceral, depending on the specific anatomical structure that is afflicted. Neuropathic pain refers to any form of pain resulting from injury or impairment to the somatosensory nerve system (Finnerup et al., 2016). The pain associated with cancer frequently exhibits a combination of nociceptive and neuropathic pathology. An instance of nociceptive pain has the potential to induce further harm to the somatosensory nerve system, hence leading to a partially neuropathic pain experience (Caraceni & Shkodra, 2019).

In addition to pain originating from the affected tissue, cancer pain may also arise as a result of chemotherapy treatment. One potential therapy option is the use of paclitaxel. Paclitaxel is a chemotherapeutic drug generated from taxanes that is commonly used as a first-line treatment for breast and ovarian cancer. Peripheral neuropathy is identified as the primary dose-limiting adverse effect of paclitaxel, as a result of the absence of preventative or therapeutic approaches (Dougherty et al., 2004). Numbness, tingling, spontaneous discomfort, and pain resulting from mechanical stimulation and exposure to cold frequently manifest in the extremities, namely the hands and feet. A meta-analysis shows that the administration of paclitaxel has been found to result in peripheral neuropathy in a range of 44% to 98% of patients (Seretny et al., 2014). The duration of neuropathy following paclitaxel administration might extend for a prolonged period ranging from several months to even years. Therefore, the administration of paclitaxel induces sensory anomalies and persistent discomfort, leading to a decrease in the overall quality of life.

World Health Organization (WHO) introduced the idea of pain management in 1986, which involves a three-step method referred to as a "ladder." This treatment strategy emphasizes the appropriate use of medications and their administration through titration. WHO subsequently revised the concept into a four-step framework, which involves the integration of pharmaceutical methods for pain management with a focus on patient-centered care, interdisciplinary approaches, complementary therapies, and integrative medicine (Vargas-Schaffer & Cogan, 2014).

First-tier analgetic has a "ceiling effect" on their analgesia effect, which means that exceeding the maximum dose will result in the loss of the desired analgesia effect. There are several choices of analgesic drugs that can be used at level one such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). Analgesics in the second and third tiers encompass the inclusion of opioids within their composition. Opioids, namely codeine, hydrocodone, hydromorphone, morphine, and oxycodone, have comparable pharmacokinetic and pharmacodynamic profiles. Tier four includes interventional therapy. This therapeutic intervention encompasses a spectrum of approaches, ranging from basic nerve blocks to more advanced regional or neurolytic blocks, and in some cases, even necessitating neurosurgical interventions. Lastly, complementary therapy. Complementary treatments are classified as non-mainstream methods that are employed alongside traditional therapy. The prevailing supplementary therapies encompass herbal supplements and pharmaceuticals, chiropractic practices, yoga, massage therapy, and acupuncture.

Kynurenic acid

KYNA is synthesized in several organs, with a notable concentration in the liver, through the enzymatic activity of tryptophan dioxygenase (TDO) and 2,3-dioxygenase (IDO). The presence of pro-inflammatory cytokines leads to the metabolic conversion of tryptophan (TRP) into KYNA. The levels of KYNA in the central nervous system experience an elevation through a method that is not reliant on the expression of IDO. This mechanism involves an enhanced transportation of KYNA to the brain during instances of systemic inflammation. The activation of IDO is known to be impacted by pro-inflammatory cytokines, which in turn can lead to the experience of pain and the manifestation of depressive-like behavior in the context of inflammation. The induction of CP is associated with the manifestation of depression-like behavior, which is accompanied by an increase in IDO expression in the hippocampus through the overexpression of interleukin-6 (IL-6) (Savitz, 2020). It is well-established that disruptions in the central nervous system frequently coincide with disruptions in TRP metabolism. The products derived from the kynurenine pathway play a crucial role in the intrinsic control of neuronal excitability and also serve as mediators for immune cell responses. KYNA and quinolinic acid are two metabolites that have garnered significant interest due to their divergent effects. Quinolinic acid (QUIN) is a compound that has modest potency as an agonist of the NMDA receptor, displaying specificity towards this receptor subtype. Conversely, KYNA is an endogenous antagonist that lacks selectivity, acting on all subtypes of glutaminergic receptors involved in the transmission of pain signals. Hence, the kynurenine pathway may be categorized into two main branches: KYNA, which has neuroprotective properties, and QUIN, which is associated with neurotoxicity (Ciapała et al., 2021). Nevertheless, it is noteworthy that contemporary studies have revealed that metabolites of the TRP-KYN pathway possess Janus face characteristics, implying their ability to exhibit both advantageous and detrimental effects contingent upon the dosage or circumstances (Wirthgen et al., 2018).

The existence of KYNA in the blood serum of humans has been consistently documented. The concentration of KYNA in the serum collected from healthy adult individuals ranges from 16-71 nmol/l and this range remains consistent in the serum collected from youngsters (Turska et al., 2022). The level of KYNA rises proportionally with the intensity of pain (Athnaiel et al., 2022; Waloejo et al., 2022). However, a study found that primary cervical cancer has a mean level of KYNA was less than half of their control (250 nmol/l vs. 550 nmol/l) (Fotopoulou et al., 2011). Yet another study also found that TRP metabolites are lower in patients with inflammatory-induced pain, this is probably because TRP metabolites are metabolized in KYN pathway for reducing pain (Barjandi et al., 2020). Nevertheless, the concentration of KYNA was shown to be elevated in the bloodstream of individuals afflicted with multiple sclerosis, inflammatory bowel disease, and type 2 diabetes. In

contrast, the levels of KYNA were shown to be reduced in patients diagnosed with chronic schizophrenia, Alzheimer's dementia, cluster headaches, chronic migraines, and Parkinson's disease (Ciapała et al., 2021).

There is no information on KYNA's role in acute pain, however, there is plenty of information on how the KYN pathway contributes to the production of important cytokines in the incidence of CP (Gunn et al., 2020).

Acupuncture

Acupuncture, an ancient therapeutic practice, has been employed in China for many centuries as a means to alleviate diverse forms of pain. The analgesic effect of acupuncture is initiated by the stimulation of certain acupuncture sites, characterized by their distinctive anatomical composition. Acupuncture sites encompass several dynamic components, including mast cells, blood vessels, and nerve fibers, which play a crucial role in mediating the effects of acupuncture. Acupuncture subsequently transmits messages to the spinal cord and other regions of the brain. This phenomenon has the potential to either augment or diminish the levels of diverse neurotransmitters, modulators, and constituents that possess analgesic properties (Chen et al., 2020). The act of inserting acupuncture needles into the body elicits stimulation of nerve A fibers located in the skin, as well as type II/III fibers situated within the muscles. The process of needling will elicit a response from free nerve terminals, resulting in the generation of action potentials. These action potentials will propagate within the nerve network, referred to as axon reflexes, leading to the occurrence of vasodilation and subsequent augmentation of blood circulation in the immediate area (Coutaux, 2017). The activation of A nerve fibers and type II/III fibers results in their projection towards the transmission cells located in the posterior horn of the spinal cord. Additionally, these fibers will also establish collateral connections with the intermediate cells. The release of enkephalin by intermediate cells inhibits pain transmission from substantia gelatinosa cells, which are involved in the nociceptive pathway of unmyelinated C nerve fibers (Chen et al., 2020).

When acupuncture needles are put in, they send pain signals through the spinothalamic tract. Signals will be sent from the brain stem to the periaqueductal gray (PAG), which will then send them to the nucleus raphe magnus (NRM). Then, serotoninergic fibers come down from this center and send serotonin to intermediate cells in the posterior horn of the spinal cord that have already been turned on by the effects of segmental acupuncture. Serotonin then tells the intermediate cells to release met-enkephalin, which, like the segmental process, stops the substantia gelatinosa cells from growing. This action will make the already active segmental pain reduction even stronger. This makes acupuncture work even better at reducing pain. Through the brain, acupuncture also affects the anterior pituitary, which then lets out endorphins into the bloodstream. Endorphins are also sent to the PAG by nerve fibers that come down from the arcuate nucleus in the brain. This area controls pain, fear, and anxiety. The limbic structures, which include the amygdala, hippocampus, para-hippocampus, anterior cingulate cortex, prefrontal cortex, septum, nucleus accumbens, hypothalamus, insula, and caudate, will then receive signals from the thalamus. The limbic system's signal intensity can be decreased by acupuncture needle insertion, according to magnetic resonance imaging (MRI) imaging. This demonstrates how acupuncture can affect the emotional aspect of pain, calming the patient's emotions and promoting relaxation (White et al., 2008).

Previous studies have demonstrated that acupuncture has a notable impact on the metabolism of TRP, resulting in a considerable drop in TRP levels but enhances the levels and activity of QUIN, KYN, and IDO (Zhang et al., 2020). Another study has demonstrated that acupuncture has the potential to elevate the levels of KYN and QUIN, while concurrently reducing the levels of KYNA (Bao et al., 2021). This phenomenon is likely attributable to the capacity of acupuncture to augment TRP metabolism, leading to improved absorption of TRP metabolites and subsequent pain reduction.

5. Discussion

The results of this study shed light on the complex interplay between CP, KYNA and acupuncture. CP, whether nociceptive or neuropathic, has a multifaceted pathophysiological progression, involving various peripheral and central mechanisms. The modulation of pain pathways is crucial for alleviating discomfort, as persistent acute pain can lead to allodynia, hyperalgesia, and hyperpathia, impairing normal functioning. Understanding the mechanisms of pain is essential for developing effective treatments.

KYNA a metabolite of TRP, emerges as a significant player in this context. Its levels in the central nervous system are influenced by inflammation and can impact pain perception and depressive-like behavior. KYNA's Janus-faced nature, acting as an antagonist on glutaminergic receptors involved in pain transmission, highlights its potential role as a biomarker for pain severity and treatment outcomes.

Acupuncture, a traditional therapeutic practice, is explored as a means of pain management. It activates nerve fibers and triggers complex pathways, including the release of enkephalins and endorphins, which modulate pain perception. Acupuncture also affects TRP metabolism, potentially elevating levels of KYNA's neurotoxic counterpart, quinolinic acid, while reducing KYNA itself. These findings suggest that acupuncture may offer a unique approach to pain modulation, with implications for KYNA levels and pain relief.

In summary, this study provides valuable insights into the intricate relationship between CP, KYNA, and acupuncture. It underscores the need for further research to elucidate the precise mechanisms involved and to explore the potential of acupuncture as a complementary therapy for CP conditions by considering its impact on KYNA and associated TRP metabolites.

6. Conclusion

Acupuncture, as a supplemental therapeutic intervention, has the potential to mitigate the reliance on opioids among individuals with CP, given the substantial risk associated with the adverse consequences of opioid usage. The biomarker KYNA has the potential to be utilized for objective evaluation of many forms of CP, including cancer-related pain. In conclusion, acupuncture has demonstrated efficacy in alleviating CP, and the objective assessment of its effectiveness can be facilitated by the utilization of KYNA. Further investigation is required to deepen our comprehension of acupuncture, KYNA, and their interplay in CP. These areas of inquiry possess the capacity to enhance our knowledge of CP, with a specific emphasis on alleviating cancer-related pain.

Conflict of interest: The authors report no conflicts of interest in this work.

Reverences

1. Athnaiel, O., Ong, C., & Knezevic, N. N. (2022). The Role of Kynurenine and Its Metabolites in Comorbid Chronic Pain and Depression. *Metabolites*, *12*(10), 950. https://doi.org/10.3390/metabo12100950
2. Bao, C.-H., Zhong, J., Liu, H.-R., Gu, Y.-P., Wu, P., Gu, K., Wang, D., Weng, Z.-J., Shi, Y., & Wu, H.-G. (2021). [Effect of acupuncture-moxibustion on negative emotions and plasma tryptophan metabolism in patients with Crohn's disease at active stage]. *Zhongguo Zhen Jiu = Chinese Acupuncture & Moxibustion*, *41*(1), 17–22. https://doi.org/10.13703/j.0255-2930.20200814-k0003
3. Barjandi, G., Louca Jounger, S., Löfgren, M., Bileviciute-Ljungar, I., Kosek, E., & Ernberg, M. (2020). Plasma tryptophan and kynurenine in females with temporomandibular disorders and fibromyalgia—An exploratory pilot study. *Journal of Oral Rehabilitation*, *47*(2), 150–157. https://doi.org/10.1111/joor.12892
4. Bruera, E., & Kim, H. N. (2003). Cancer pain. *JAMA*, *290*(18), 2476–2479. https://doi.org/10.1001/JAMA.290.18.2476
5. Caraceni, A., & Shkodra, M. (2019). Cancer Pain Assessment and Classification. *Cancers 2019, Vol. 11, Page 510*, *11*(4), 510. https://doi.org/10.3390/CANCERS11040510
6. Chapman, S. (2011). Assessment and management of patients with cancer pain. *Cancer Nursing Practice*, *10*(10), 28–37. https://go.gale.com/ps/i.do?p=AONE&sw=w&issn=14754266&v=2.1&it=r&id=GALE%7CA275850626&sid=googleScholar&linkaccess=fulltext
7. Chapman, S. (2012). Cancer pain part 1: causes and classification. *Nursing Standard (Royal College of Nursing (Great Britain) : 1987)*, *26*(47), 42–46. https://doi.org/10.7748/NS2012.07.26.47.42.C9224
8. Chen, T., Zhang, W. W., Chu, Y. X., & Wang, Y. Q. (2020). Acupuncture for Pain Management: Molecular Mechanisms of Action. *Https://Doi.Org/10.1142/S0192415X20500408*, *48*(4), 793–811. https://doi.org/10.1142/S0192415X20500408
9. Ciapała, K., Mika, J., & Rojewska, E. (2021). The Kynurenine Pathway as a Potential Target for Neuropathic Pain Therapy Design: From Basic Research to Clinical Perspectives. *International Journal of Molecular Sciences*, *22*(20), 11055. https://doi.org/10.3390/ijms222011055

10. Cohen, M., Quintner, J., & Van Rysewyk, S. (2018). Reconsidering the International Association for the study of pain definition of pain. *Pain Reports*, *3*(2). https://doi.org/10.1097/PR9.0000000000000634
11. Coutaux, A. (2017). Non-pharmacological treatments for pain relief: TENS and acupuncture. *Joint Bone Spine*, *84*(6), 657–661. https://doi.org/10.1016/J.JBSPIN.2017.02.005
12. Dahlhamer, J., Lucas, J., Zelaya, , Carla, Nahin, R., Mackey, S., DeBar, L., Kerns, R., Von Korff, M., Porter, L., & Helmick, C. (2018). Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016. *MMWR. Morbidity and Mortality Weekly Report*, *67*(36), 1001–1006. https://doi.org/10.15585/mmwr.mm6736a2
13. Dougherty, P. M., Cata, J. P., Cordella, J. V., Burton, A., & Weng, H. R. (2004). Taxol-induced sensory disturbance is characterized by preferential impairment of myelinated fiber function in cancer patients. *Pain*, *109*(1–2), 132–142. https://doi.org/10.1016/j.pain.2004.01.021
14. Finnerup, N. B., Haroutounian, S., Kamerman, P., Baron, R., Bennett, D. L. H., Bouhassira, D., Cruccu, G., Freeman, R., Hansson, P., Nurmikko, T., Raja, S. N., Rice, A. S. C., Serra, J., Smith, B. H., Treede, R. D., & Jensen, T. S. (2016). Neuropathic pain: An updated grading system for research and clinical practice. *Pain*, *157*(8), 1599–1606. https://doi.org/10.1097/J.PAIN.0000000000000492
15. Fischer, D. J., Villines, D., Kim, Y. O., Epstein, J. B., & Wilkie, D. J. (2010). Anxiety, depression, and pain: differences by primary cancer. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer*, *18*(7), 801–810. https://doi.org/10.1007/S00520-009-0712-5
16. Fotopoulou, C., Sehouli, J., Pschowski, R., VON Haehling, S., Domanska, G., Braicu, E.-I., Fusch, G., Reinke, P., & Schefold, J. C. (2011). Systemic changes of tryptophan catabolites via the indoleamine-2,3-dioxygenase pathway in primary cervical cancer. *Anticancer Research*, *31*(8), 2629–2635.
17. Green, C. R., & Hart-Johnson, T. (2010). Cancer pain: an age-based analysis. *Pain Medicine (Malden, Mass.)*, *11*(10), 1525–1536. https://doi.org/10.1111/J.1526-4637.2010.00957.X
18. Gunn, J., Hill, M. M., Cotten, B. M., & Deer, T. R. (2020). An Analysis of Biomarkers in Patients with Chronic Pain. *Pain Physician*, *23*(1), E41–E49.
19. Gutgsell, T., Walsh, D., Zhukovsky, D. S., Gonzales, F., & Lagman, R. (2003). A prospective study of the pathophysiology and clinical characteristics of pain in a palliative medicine population. *The American Journal of Hospice & Palliative Care*, *20*(2), 140–148. https://doi.org/10.1177/104990910302000213
20. Haefeli, M., & Elfering, A. (2006). Pain assessment. *European Spine Journal*, *15*(SUPPL. 1), S17–S24. https://doi.org/10.1007/S00586-005-1044-X/METRICS
21. Jovanovic, F., Candido, K. D., & Knezevic, N. N. (2020). The Role of the Kynurenine Signaling Pathway in Different Chronic Pain Conditions and Potential Use of Therapeutic Agents. *International Journal of Molecular Sciences*, *21*(17), 6045. https://doi.org/10.3390/ijms21176045
22. Nicholas, M., Vlaeyen, J. W. S., Rief, W., Barke, A., Aziz, Q., Benoliel, R., Cohen, M., Evers, S., Giamberardino, M. A., Goebel, A., Korwisi, B., Perrot, S., Svensson, P., Wang, S.-J., & Treede, R.-D. (2019). The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain*, *160*(1), 28–37. https://doi.org/10.1097/j.pain.0000000000001390
23. Savitz, J. (2020). The kynurenine pathway: a finger in every pie. *Molecular Psychiatry*, *25*(1), 131–147. https://doi.org/10.1038/s41380-019-0414-4
24. Seretny, M., Currie, G. L., Sena, E. S., Ramnarine, S., Grant, R., Macleod, M. R., Colvin, L. A., & Fallon, M. (2014). Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain*, *155*(12), 2461–2470. https://doi.org/10.1016/J.PAIN.2014.09.020
25. Sherwood, L. (2016). *Human physiology : from cells to systems* (9th ed., Vol. 1). Cengage Learning.
26. Turska, M., Paluszkiewicz, P., Turski, W. A., & Parada-Turska, J. (2022). A Review of the Health Benefits of Food Enriched with Kynurenic Acid. *Nutrients*, *14*(19), 4182. https://doi.org/10.3390/nu14194182
27. van den Beuken-van Everdingen, M. H. J., de Rijke, J. M., Kessels, A. G., Schouten, H. C., van Kleef, M., & Patijn, J. (2007). Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Annals of Oncology : Official Journal of the European Society for Medical Oncology*, *18*(9), 1437–1449. https://doi.org/10.1093/ANNONC/MDM056
28. Vargas-Schaffer, G., & Cogan, J. (2014). Patient therapeutic education: placing the patient at the centre of the WHO analgesic ladder. *Canadian Family Physician Medecin de Famille Canadien*, *60*(3), 235–241. http://www.ncbi.nlm.nih.gov/pubmed/24627377

29. Voscopoulos, C., & Lema, M. (2010). When does acute pain become chronic? *British Journal of Anaesthesia*, *105*, i69–i85. https://doi.org/10.1093/bja/aeq323
30. Waloejo, C. S., Rehatta, N. M., Andriyanto, L., Sulistiawan, S. S., Pudjirahardjo, W. J., Farhan, A. B., Kurniasari, H., & Chen, Y.-H. (2022). Kynurenic acid as chronic pain biomarker for future cancer pain management. *International Journal of Health Sciences*, 6020–6032. https://doi.org/10.53730/ijhs.v6nS5.11277
31. White, A., Cummings, M., & Filshie, J. (2008). An Introduction to Western Medical Acupuncture. *An Introduction to Western Medical Acupuncture*. https://doi.org/10.1016/B978-0-443-07177-5.X0001-3
32. Wirthgen, E., Hoeflich, A., Rebl, A., & Günther, J. (2018). Kynurenic Acid: The Janus-Faced Role of an Immunomodulatory Tryptophan Metabolite and Its Link to Pathological Conditions. *Frontiers in Immunology*, *8*. https://doi.org/10.3389/fimmu.2017.01957
33. Yong, R. J., Mullins, P. M., & Bhattacharyya, N. (2022). Prevalence of chronic pain among adults in the United States. *Pain*, *163*(2), e328–e332. https://doi.org/10.1097/j.pain.0000000000002291
34. Zhang, K., Liu, R., Gao, Y., Ma, W., & Shen, W. (2020). Electroacupuncture Relieves LPS-Induced Depression-Like Behaviour in Rats Through IDO-Mediated Tryptophan-Degrading Pathway . *Neuropsychiatric Disease and Treatment*, *Volume 16*, 2257–2266. https://doi.org/10.2147/NDT.S274778