World Cancer Research Journal WCRJ 2023; 10: e2479

ACUPUNCTURE APPLICATION FOR CANCER PAIN MANAGEMENT AND ITS UNDERLYING MECHANISMS

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Abstract – *Objective:* *To examine the applications of acupuncture for cancer pain management and the underlying molecular mechanisms.*

Materials and Methods: *This narrative review was performed by collecting clinical trials, basic research, and reviews on acupuncture for cancer pain treatment. Articles published in peer-reviewed scientific journals were included. Manuscripts not written in the English language were excluded. We researched PubMed, Web of Science, and Cochrane databases using keywords or combinations of the keywords: "cancer pain" and "acupuncture". Articles published between 1 January 1989 and 8 August 2022 were selected. We further screened articles from peer-reviewed scientific journals that were written in English. We searched for relevant articles based on the title and abstract of the retrieved scientific outcome. The articles that potentially fit our aim were finally discussed.*

Results: *An amount of 1318 articles were included in the initial search. After the remotion of 200 manuscripts before the screening and the exclusion of non-pertinent 50 articles, and 30 review papers, as well as letters (n=27), proceeding papers (n=24), and other papers (n=72), 915 articles were selected and discussed in the review. For narrative aims, we divided the discussion into two paragraphs "Acupuncture-induced Analgesic Mechanisms in Cancer Pain" and "Efficacy and Safety of Acupuncture in Cancer Pain Treatment".*

Conclusions: *Given that cancer pain management requires a multimodal approach that involves a combination of pharmacological approaches with non-pharmacological strategies, acupuncture has interesting potential applications.*

KEYWORDS: *Pain, Cancer pain, Breakthrough cancer pain, Complementary therapies, Acupuncture.*

INTRODUCTION

In cancer patients, pain is one of the most frequent and disabling symptoms. Its prevalence ranges from about 33% in the early stages of the disease to up 75% in the more advanced and terminal stages[1]. Moreover, cancer pain management is a challenge for clinicians and a commitment of resources for the healthcare system. This challenge is the result of a multitude of pathophysiological processes that must be fully characterized. According to the 11th revision of the International Classification of Diseases (ICD) released by the task force of the International Association for

DOI: 10.32113/wcrj_20231_2479

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the Study of Pain (IASP), chronic cancer pain is a subset of chronic secondary pain produced by primary cancer itself or metastases or its therapy[2]. Consequently, a schematic approach following the analgesic scale the WHO proposed in 1986 can be very reductive[3]. In recent years, the concept of pain has evolved, and several studies have highlighted the role of brain structures in its genesis and maintenance. Pain is no longer seen as a linear experience directly induced by sensory inputs evoked by the stimulation of nociceptors ("nociception"), but it is a multidimensional experience due to the activation of a diffuse brain network (Pain Matrix). This activation involves a widely distributed neural network[4]. Furthermore, the view of chronic cancer pain as a "biopsychosocial disease" is now widely accepted. According to this model, pain is a unique experience with a multifactorial genesis. In other words, it is the result of a dynamic experience, highly variable in a space-time way[5,6].

Therefore, there is a need to rethink the concept of pain management, which is increasingly characterized as "precision medicine" aimed at developing personalized therapy. Consequently, the treatment of chronic oncological pain syndrome must follow a multimodal approach, using pharmacological and non-pharmacological strategies.

Interestingly, good outcomes on the use of complementary alternative medicine (CAM) including acupuncture as medical practice, but also natural compounds (e.g., probiotics, herbs, minerals, vitamins), have been widely reported in literature[7-9]. According to a new concept of integrative medicine, in the cancer setting, therapeutic strategies can be combined and tailored to each patient[10]. Notably, in patients treated with CAM, an improved health-related quality of life (HR-QoL) was also described[11].

Although several reports are available in the literature[12] the use of acupuncture for the management of cancer pain must be properly studied. There is a need to evaluate the application of this non-pharmacological strategy in different clinical settings.

On these bases, in this narrative review, we address the applications of acupuncture for cancer pain management.

MATERIALS AND METHODS

This narrative review was performed by collecting clinical trials, basic research, and reviews on acupuncture for cancer pain treatment. Articles published in peer-reviewed scientific journals were included. Articles were excluded if they were not written in the English language. We researched PubMed, Web of Science, and Cochrane databases using keywords or combinations of the keywords: "cancer pain" and "acupuncture". Articles published between 1 January 1989 and 8 August 2022 were selected. We further screened articles from peer-reviewed scientific journals that were written in English. We searched for relevant articles for further reading based on the title and abstract. We read the articles that potentially fit our aim and these papers were discussed in the present review.

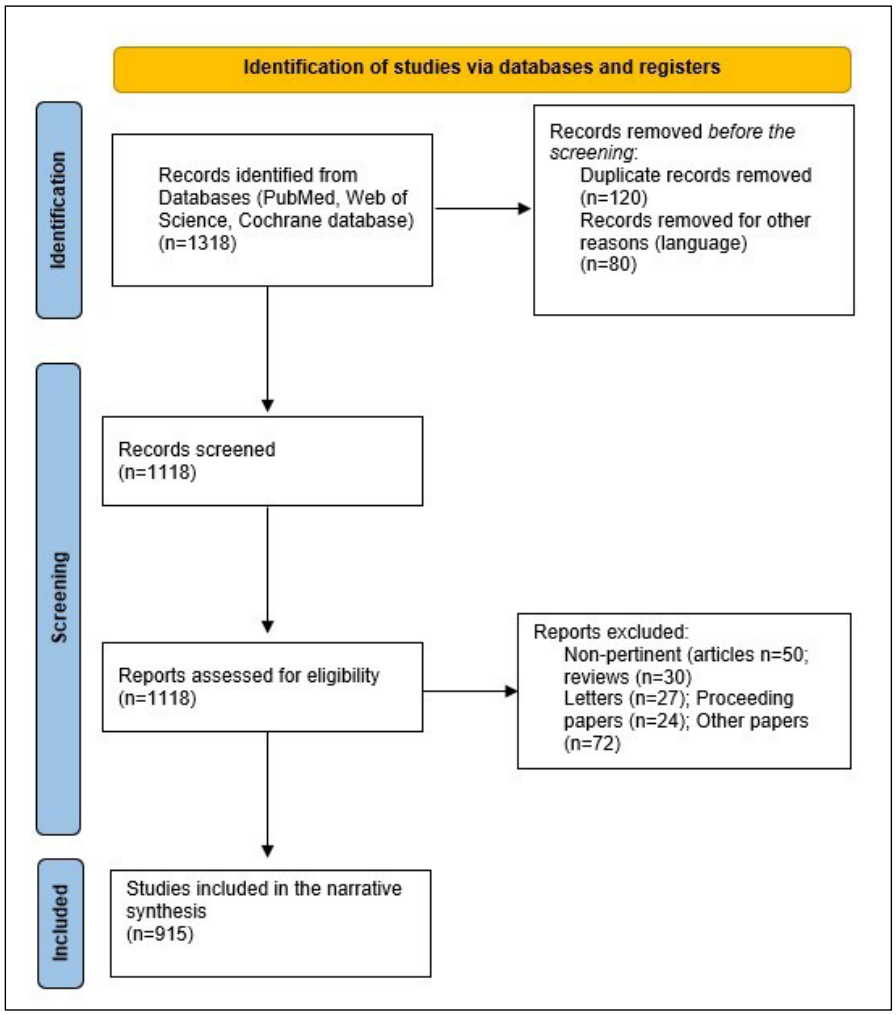
RESULTS

An amount of 1318 articles were included in the initial search. After the remotion of 200 manuscripts before the screening and the exclusion of non-pertinent 50 articles, and 30 review papers, as well as letters (n=27), proceeding papers (n=24), and other papers (n=72), 915 articles were selected and discussed in the review (Figure 1). The annual trend in the scientific output is shown in Figure 2. For narrative aims, we divided the discussion into two paragraphs: "Acupuncture-induced Analgesic Mechanisms in Cancer Pain" and "Efficacy and Safety of Acupuncture in Cancer Pain Treatment"

Acupuncture-induced Analgesic Mechanisms in Cancer Pain

Research suggested that acupuncture activates the neuro-endocrine response of the human body orchestrated by central and peripheral mechanisms[13-15]. Nevertheless, the proposed mechanisms of action of acupuncture against cancer pain are complex and not fully elucidated. At the peripheral level, acupuncture stimulates the inflammation cells to produce endogenous opioids capable of targeting the nerve fibers. Through this mechanism, two effects are produced: direct analgesia and reduction of hyperalgesia. Different studies have shown that, by stimulating specific points, acupuncture activates different zones in the central nervous system (CNS) thus reducing pain. Consequently, endogenous antinociceptive neurotransmitters such as noradrenaline, dopamine, adenosine, endocannabinoids, and others are released[16-19]. Additionally, different studies performed through diagnostic imaging techniques in patients subjected to acupuncture highlighted its role in pain control by acting at different somatosensory, affective, and cognitive brain regions[20,21]. Moreover, it has been shown that acupuncture suppresses neurodegeneration by interfering with

Fig. 1. PRISMA flow chart.



specific signaling pathways mostly involving the brain-derived neurotrophic factor (BDNF) and the neurotrophin (NT) family of proteins[22]. It has been also demonstrated that acupuncture exerts its analgesic effects by inhibiting the proinflammatory cytokines, the proinflammatory neuropeptides, and neurotrophins, through the modulation of transient receptor potential valloniid (TRPV1)[23].

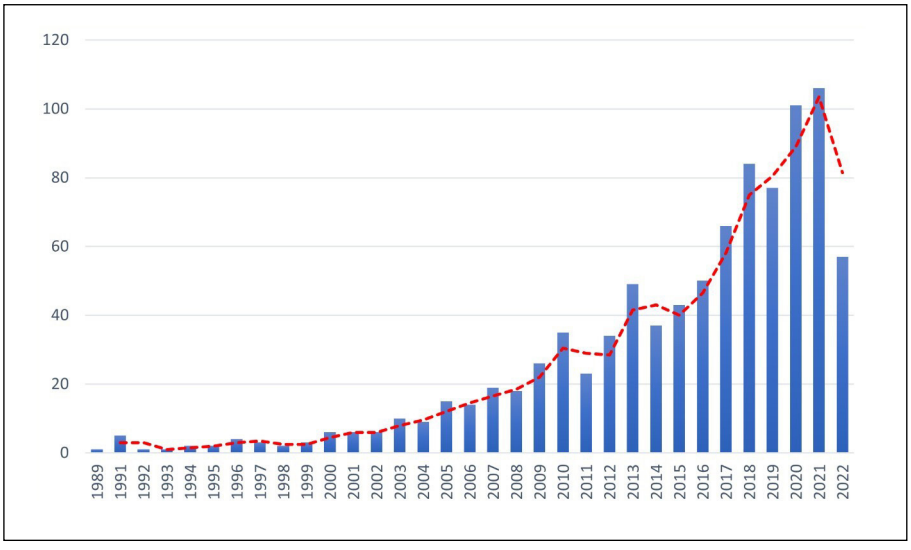


Fig. 2. Annual trend of selected and discussed publications.

TABLE 1. The search strategy.

Item	*Specification*
Date of search	June 2022 through 8 August 2022
Databases and other sources selected	PubMed, Web of Science, Cochrane database
Search terms used	"cancer pain" and "acupuncture"
Time frame	January 1989 to 8 August 2022
Inclusion and exclusion criteria	English articles only, duplicates excluded
Selection process	Three independent investigators familiar with cancer pain and acupuncture

TABLE 2. Acupuncture-induced Analgesic Mechanisms in Cancer Pain.

Mechanisms	*Effects*	*References*
Mechanical signal to connective tissue cells via mechano-transduction after reaction to acupuncture needling 'de qi'	Releases of growth factors, cytokines, vasoactive substances, degradative enzymes, and structural matrix elements. Influences on the extracellular surrounding connective tissue cells. Changes in matrix composition Modulates the signal transduction to and within the cell.	Langevin et al[13] (2001)
Neurobiological	Increases local blood flow, facilitated healing, and analgesia. Affects pain-modulating neurotransmitters such as met-enkephalin and substance P along the nociceptive pathways.	Cheng et al[14] (2014)
	Provides immediate and safe pain relief in neuropathic cancer breakthrough pain by neuromodulating effects on the spinal and central nervous levels.	Huemer et al[16] (2022)
	Releases specific neuropeptides in the CNS; elicits profound physiological effects and activates self-healing mechanisms.	Han et al[19] (2003)
	Activates supramarginal gyrus, SII, pre-SMA, middle cingulate gyrus, insula, thalamus, and precentral gyrus. Deactivates pregenual anterior cingulate, subgenual cortex, amygdala/hippocampal formation, vmPFC, nucleus accumbens and PCC.	Huang et al[20] (2012)
	Neuroprotective effects via expression and activation of BDNF and NT.	Lin et al[22] (2014)
	Downregulates proinflammatory neuropeptides, SP, and VIP, EA; proinflammatory cytokines STAT 6 and NFκB, and neurotrophins; Upregulates CXCL10, increases the production and the release of CXCR3+ macrophages containing opioids and inhibits the release of proinflammatory cytokines, CCL2, CCL3, and CXCL8. Activates cholinergic anti-inflammatory pathway involving acetylcholine release from vagus nerves binding to α7-nicotinic receptors (α7-nAChRs) on macrophages, thereby inhibiting the release of proinflammatory cytokines.	Mc Donald et al[23] (2015)
	Modulates TRPV1. Activates ST36 and relieves inflammation through vagus nerve activation, TLR4/NF-κB signaling, MAPK signaling pathway, and cholinergic anti-inflammatory pathways.	Oh et al 24 (2022)

Abbreviations: CNS: central nervous system; pre-SMA: pre-supplementary motor area; vmPFC: ventromedial prefrontal cortex, SII: secondary somatosensory cortex; PCC: posterior cingulate cortex; NT: neurotrophin; BDNF: brain derived neurotrophic factor; TRPV1: transient receptor potential vallinoid; ST36: Zusanli; α7-nAChRs: α7-nicotinic receptors; STAT 6: activator of transcription 6; NFκB; nuclear factor kappa B (B); SP: substance P; VIP: vasoactive intestinal peptide; EA: CXCL10: C-X-C motif chemokine ligand 10; CCL:2: C-C Motif Chemokine Ligand 2; CCL83: C-C Motif Chemokine Ligand 3; CXCL8: C-X-C Motif Chemokine Ligand 8; TLR4: like receptor 4; MAPK: mitogen-activated protein kinase.

The central mechanism of acupuncture-induced analgesia concerns the enhancement of the endogenous opioid system. This action provides for a reduction of the nociceptive stimulus at the spinal level, with the involvement of various molecules such as dynorphins and enkephalins. In both central and peripheral mechanisms, one of the most involved points is Zusanli (ST36)[24]. Remarkably, it is one of the points used in Traditional Chinese Medicine as a general rebalancing of homeostasis. Moreover, experimental studies have shown that the stimulation of certain points by acupuncture activates several centers in the CNS (e.g., periaqueductal grey matter, locus coeruleus, nuclei raphe Magnus, and rostral ventromedial medulla), resulting in the activation of pain inhibition mechanisms and subsequent release of endogenous antinociceptive neurotransmitters, including endorphins. However, the opioid system alone does not explain the analgesic action of acupuncture. Other chemical mediators and supraspinal structures are involved. Among the chemical mediators, cannabinoids certainly deserve mention[25]. Following acupuncture, the cannabinoid system reacts with an upregulation of its receptors with a consequent increase in the opioid release.

Efficacy and Safety of Acupuncture in Cancer Pain Treatment

Acupuncture is considered an effective treatment in patients with non-cancer pain conditions such as low back pain or pain associated with knee osteoarthritis[15]. Furthermore, several clinical studies have been conducted to test the efficacy and safety of acupuncture in the treatment of cancer pain patients. Data from these studies were also collected and analyzed in many systematic reviews and meta-analyses[26-32]. Results are often contradictory, probably due to the insufficient number of studies (and patients) and/or the scarce quality of the studies. For example, in a meta-analysis on the effectiveness and safety of acupuncture for patients suffering from cancer pain, Hu et al[27] demonstrated that acupuncture potentiated the effects of the analgesic drug therapy administered in accordance with the World Health Organization recommendations. Moreover, acupuncture ameliorated the HRQoL of cancer patients. Later, Chiu et al[28] by revising 36 trials conducted on cancer patients suffering from different types of pain (cancer-related pain; chemotherapy-induced, radiotherapy-induced pain, or hormone-induced pain) and showed that acupuncture slightly ameliorated pain caused by surgery. On the contrary, no efficacy was observed in patients with pain induced by radiotherapy and chemotherapy. Finally, no sufficient outcomes were described for the effectiveness of acupuncture in patients with pain induced by hormone treatment. The authors also proved that a limited number of patients treated by acupuncture developed side effects (e.g., subcutaneous hemorrhages, petechiae, etc.). In another study, He et al[29] demonstrated that acupuncture significantly reduced cancer pain and can limit the use of analgesics. Subsequently, Yang et al[30] published a systematic review of randomized clinical trials on the role of acupuncture in the treatment of cancer-related pain. The authors concluded that acupuncture could represent an effective and safe therapy in alleviating pain symptoms. Otherwise, they highlighted the need for more high-quality studies to confirm these findings.

Acupuncture can be a useful strategy against drug-induced side effects. For example, in a systematic review and meta-analysis, Han et al[31] published data elaborated on the application of acupuncture, with or without medication, in cancer patients who experienced opioid-induced constipation (OIC). Results indicated that this integrative approach was effective in the treatment of OIC, mainly in combination with drugs. Recently, Iskandarani et al[32] revised the randomized controlled trials conducted to highlight the role of acupuncture in the management of symptoms that occurred in patients with hematologic cancer. Data collected suggested convincing evidence that acupuncture is strongly able to reduce pain as well as nausea and vomiting in treated patients.

Different clinical studies demonstrated that acupuncture is effective in cancer patients with chemotherapy-induced peripheral neuropathy (CIPN) and other types of therapy-induced neurotoxicity[33-39]. CIPN is provoked by anticancer agents such as platinum compounds, taxanes, vinca alkaloids, bortezomib, and thalidomide. The syndrome may develop with persistent severe symptoms including pain, dysesthesias, numbness, tingling, and autonomic neuropathy. Thus, in patients with CIPN, standard anti-neuropathic pharmacotherapy can be not effective and, consequently, symptoms can negatively affect the HRQoL. In clinical practice, due to its ease of use and safety, acupuncture may be recommended for patients with CIPN, particularly those who do not benefit from standard pharmacotherapy[30]. Nevertheless, clinical results are contradictory. Although two clinical studies demonstrated the efficacy of this treatment by ameliorating analgesic efficacy and HRQoL[34,35] in another investigation, Lu et al[36] showed the ineffectiveness of acupuncture against pain and for ameliorating the HRQoL. However, the effectiveness of acupuncture was reported by other clinical studies. Zhi et al[37] found that acupuncture ameliorated several symptoms associated with bortezomib-induced CIPN. Probably, the results should be validated by additional studies.

Recently, Jin et al[40] published an interesting review on acupuncture. They considered clinical trials enrolling cancer patients and offered new insight for more precise studies in the clinical scenario of acupuncture therapy for cancer pain and other cancer-induced phenomena. Finally, Ge et al[41] elaborated an evidence-based guideline on acupuncture use for the management of cancer patients suffering from moderate to severe pain. Basically, the authors strongly recommended acupuncture treatment. They also suggested the use of acupuncture for alleviating arthralgia induced by aromatase-inhibitor in breast cancer patients. Moreover, the authors weakly suggested combined treatments with acupressure/acupuncture to reduce pain intensity, decrease the opioid dose, and ameliorate opioid-related side effects. Unfortunately, the low-quality evidence suggests additional studies. Otherwise, this guideline should be useful for clinicians and appreciated by cancer patients suffering from pain and treated with acupuncture. Finally, a manual useful for the assessment and treatment of pain with acupuncture in hospitalized cancer patients was recently developed. It should support acupuncturists through the definitions of standardized strategies and pathways[42].

CONCLUSIONS

Cancer pain management requires a multimodal approach that involves a combination of pharmacological approaches and non-pharmacological strategies. Acupuncture is a strategy that has interesting application possibilities. This review highlighted that the mechanisms of action of acupuncture require in-depth research and more clinical trials should be necessary to increase the strength of published evidence. However, acupuncture, as a CAM method, can be used safely in cancer patients suffering from pain, especially when standard treatments are not well tolerated or are unsuccessful. Moreover, an integrative approach to cancer pain management can ameliorate, not only the quality of pain treatment, but also the HRQoL.

Ethics approved:
Not applicable

Informed consent:
Not applicable

Availability of data and material:
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study

Conflict of interest:
The authors have declared no conflict of interest.

Funding:
None.

Authors contributions:
Conceptualization M. Cascella. M. Cascella; writing—original draft preparation; S. Bimonte and M. Cascella: writing—review and editing. All Authors have read and agreed to the published version of the manuscript.

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