

Acupuncture for Management of Endodontic Emergencies: a Review

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Root canal treatment (RCT) employed for painful endodontic conditions like apical periodontitis and irreversible pulpitis is associated with a high incidence of postoperative pain. Pharmacological management for this purpose is effective, but not entirely free from side effects and in some cases may fail to provide adequate relief. Furthermore, concerns have been raised regarding the transmission of coronavirus disease-2019 (COVID-19) as a result of the aerosols generated and prolonged chair side time required for RCT. Acupuncture is a traditional Chinese therapy commonly employed as an alternative for the treatment of pain. And what's more, the use of acupuncture has been recently reported as treatment for the management of endodontic pain as well as on the anesthetic success in patients with irreversible pulpitis. This review aims to evaluate the current evidence for acupuncture in endodontics and its potential role in emergency pain relief and management for patients. To combat this, a thorough search for literature within the field was performed in five electronic databases. Retrieved studies were screened according to the pre-defined eligibility criteria. After both an electronic and manual search, five studies were selected for review. These studies reported the beneficial effects of acupuncture in reducing the failure of nerve block in patients with irreversible pulpitis and in controlling both intraoperative and postoperative pain following RCT. In addition, it was also reported to reduce anxiety surrounding the dental procedure and minimized the intake of analgesics after the endodontic procedure, which can result in some unwanted side effects. However, more in depth clinical research is required before any recommendation regarding the application of acupuncture in endodontic patients can be made.

Keywords: Acupuncture, COVID-19, Endodontics, Pain, Pulpitis, Root canal treatment

INTRODUCTION

Acupuncture is a popular alternative therapy that has evolved from the traditional Chinese medicinal practice [1]. According to the Chinese concept, the human body possesses a fine balance between two fundamental opposing life forces known as yin and yang. While the yin symbolizes dark, feminine, or moist characteristics, the yang is associated with light, masculine or dry traits [2]. In the human body, two separate circulation systems exist for yin (blood) and yang (qi) [3]. The blood flows inside the blood vessels while the qi, or chi, meaning energy, flows in "jin-luo" or meridian [1]. Obstruction in the flow of the qi leads to a disease of the organ associated with that particular meridian [3]. Therefore, it is postulated that insertion of a needle may

reverse this obstruction in the flow of the qi. This formed the fundamental therapeutic basis of acupuncture [2]. Numerous clinical studies in the past have established the beneficial role of acupuncture in the treatment of conditions like headaches [4], nausea and vomiting [5], and neuropathy [6], irrespective of the fact that western medicine has failed to corelate the existence of the qi [2]. As a result, acupuncture has gained recognition, particularly for the treatment of pain [7], including dental analgesia [8]. However, the analgesic effect of acupuncture is poorly understood and is often attributed to its ability to stimulate nerves to release endorphins and serotonin and regulate the perception of pain in the brain and spinal cord [9,10].

Endodontic pain arises from the inflammation in the pulp and periradicular root tissues triggered by microbial





invasion of the pulp of the tooth [11]. Root Canal Treatment (RCT) employed to eliminate intracanal infection of the tooth is thought to be a painful procedure. This perception may deter patients from seeking endodontic care, thereby further eliminating the possibility of retaining their natural teeth [12,13]. Management of endodontic pain has become comparatively easy and predictable with the advancement of local anesthetics [14]. However, conditions such as acute irreversible pulpitis present challenges that can prevent complete and successful anesthesia from being obtained [15]. These challenges can be due to a combination of factors including inflammation, anxiety, and anatomical obstacles encountered by the clinicians [16]. Postoperative pain after RCT is also relatively common, with an incidence as high as 58% [17]. While pharmacological and non-pharmacological approaches aim to minimize pain following non-surgical RCT, they are not always successful and may even cause other unpleasant side effects [13,18]. As previously mentioned, acupuncture is a non-pharmacological alternative therapy that may benefit endodontic patients during the intraoperative [19] and postoperative period [20]. Furthermore, in difficult cases, acupuncture could supplement local anesthetic in obtaining loss of sensation [21] and reduce analgesic intake in the postoperative period [20]. However, the application of acupuncture in endodontic procedures is still relatively uncommon. This is likely due to a limited number of studies evaluating its role in the reduction of endodontic pain.

Coronavirus Disease-2019 (COVID-19) has greatly disrupted the administration of health care services and procedures [21]. Guidelines issued by a number of regulatory bodies advised restricting aerosol-generating procedures (AGPs) like RCT, as droplets produced may lead to disease transmission and significantly increase the risk of COVID-19 infection for dentists and patients [22,23]. In the light of these advisories, acupuncture being a non-oral therapy may have the additional benefit of providing immediate relief in pain of patients where routine dental procedures can't

be administered. Therefore, the purpose of this review is to critically examine the evidence regarding the application of acupuncture for anesthetic success in endodontic patients, along with its role in managing endodontic pain.

MATERIALS AND METHODS

1. Literature search

PubMed/Medline, Ebscohost, and Cochrane CENTRAL databases were searched from inception to March 2022 using the keywords "acupuncture," "endodontics," and "root canal therapy" in various combinations (Table 1). A manual search was performed in the reference list of all the eligible studies identified after the electronic search.

2. Study selection

Electronic searches in databases returned 68 citations. In addition, we identified one study after a manual search in the reference list of the studies and standard endodontics textbooks. Next, we excluded 14 duplicates and screened 55 records. Following this, 49 records were excluded based on the title and abstract as they failed to satisfy the following inclusion criteria:

- 1. Clinical studies related to the application of acupuncture in the management of endodontic pain and dental anesthesia in human subjects.
- 2. Comparison with sham acupuncture/control/placebo.
- 3. Studies published in English language only.

The exclusion criteria of our study were case reports and review articles, and studies involving the use of acupuncture in conditions unrelated to the scope of this review.

Furthermore, one study was excluded after reading the entire article as it was a commentary on one of the included studies. Finally, five studies that met the requirements of our evaluation [3,20,24-26] were included in this review (Fig. 1).

T- C		Present and a second trans-	. d l
lable 1. Search	strategy for the	literature search in	the electronic database

Database	Search strategy	
PubMed	#1 ("acupuncture" [All Fields]) OR (acupuncture [MeSH Terms]) #2 ((((((("endodontics"[All Fields]) OR (endodontics [MeSH Terms])) OR (root canal therapy [MeSH Terms])) OR ("root canal treatment"[All Fields])) OR ("irreversible pulpitis"[All Fields])) OR ("apical periodontitis"[All Fields])) OR ("pulpitis"[MeSH Terms])) #1 AND #2	
Cochrane CENTRAL	#1 ("acupuncture") OR ("acupuncture analgesia") OR ("acupuncture"):ti,ab,kw OR (acupuncture):kw #2 ("endodontic") OR ("endodontic"):ti,ab,kw OR ("root canal treatment") OR ("root canal therapy"):ti,ab,kw OR ("root canal treatment"):kw #1 AND #2	
Ebscohost	#1 SU acupuncture OR TX acupuncture OR SU acupuncture therapy #2 SU endodontics OR TX endodontics OR SU root canal therapy #1 AND #2	



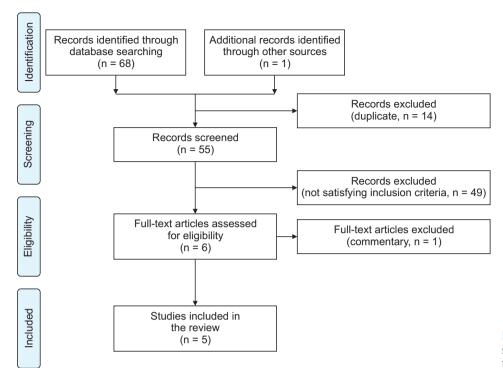


Fig. 1. The flowchart outlining studies selection procedure for the review.

CHARACTERISTICS OF THE INCLUDED STUDIES

Characteristics of the included studies are presented in Table 2. Out of five, four studies were randomized controlled trials [20,24-26], and one was a clinical study [3]. LI4, which is located at the highest point of the adductor pollicis muscle with the thumb and index finger adducted, was selected in all studies as it is considered an important acupoint for analgesic effect [27]. In addition, ST44 or Stomach 44 (Neiting), CV23 or e-Conception Vessel 23 (Lianquan), the Yintang point, ST6 or Jiache, ST7 or Xiaguan, SJ17, GB7, and GB44 were other points focused on in the included studies (Table 3).

INTERPRETATION OF INCLUDED STUDIES

Acupuncture as an emergency pain relief measure

Two studies have evaluated the effect of acupuncture on emergency pain relief in endodontic patients [24,25]. de Almeida et al. [24] assessed the efficacy of acupuncture and dipyrone for pain relief in patients with irreversible pulpitis. A total of 56 patients reporting moderate to severe pain were randomly allocated to four groups: real acupuncture, sham acupuncture, real dipyrone, and sham dipyrone. Real acupuncture was performed at four acupoints sequentially. Starting with LI4 - Large Intestine 4 (Hegu), followed by ST44 - Stomach 44 (Neiting), CV23 e-Conception Vessel 23 (Lianquan), and the Yintang point. VAS was used for

measurement of pain before and 5 minutes after intervention. The Ryodaraku method was used for measuring circulating energy, while salivary cortisol was analyzed as an objective parameter for estimating pain. The Ryodoraku method measures the circulating energy using the acupuncture device at 12 specific body points. The energy level is measured before and after an intervention to identify possible changes induced by the process. It was revealed that acupuncture provided more significant pain reduction than all other assessed groups. The mean difference in pain scores before and after interventions was 6.71, 4.25, 3, and 2.14 in real acupuncture, sham acupuncture, real dipyrone and sham dipyrone, respectively. The highest reduction of mean pain value was observed in the real acupuncture group. Murugesan et al. [25] evaluated the efficacy of acupuncture and ibuprofen for pain control in 157 patients with symptomatic irreversible pulpitis. Patients were randomly allocated to three groups that comprised classic acupuncture with placebo (CAP), sham acupuncture with placebo (SAP), and sham acupuncture with ibuprofen (SAI). A Heft-Parker visual analog scale (HPVAS) was used to measure post-treatment pain, which was recorded at 15, 30, 45, and 60 minutes. Acupoints selected in the study were LI4, ST6 (Jiache), ST7 (Xiaguan), and SJ17. The pain was significantly lower in the CAP group at all time intervals than in the other two groups. Moreover, four patients in the SAP group and five patients in the SAI group had severe pain after 60 minutes, and as a result RCT was initiated in these nine patients. In addition, the pain level in two of the patients in the SAP group did not improve after 60 minutes. Therefore,



 Table 2. Characteristics of included study

Study		Groups (n = sample	ple size)	Acupuncture points and	Practitioner	Pain	+ Q
(Year)	Clagillosis	Control	Treatment	details about needling	background	assessment	TIDGON.
Arslan (2019) [20]	Symptomatic apical periodontitis	Mock acupuncture (15) The acupuncture needle was stabilized using an adhesive bandage at the Hegu, and it didn't penetrate the skin.	Real acupuncture (15)	A disposable sterile acupuncture needle (length 25 mm, diameter 0.25 mm; Kanze) inserted 3.5- to 4.0-mm deep at Hegu was utilized for acupuncture therapy.	Specialist	Postoperative pain till the 7th day.	Significant reduction of pain in the acupuncture group (0.00) than mock acupuncture group (6.60) ($p < 0.05$).
de Almeida (2019) [24]	Irreversible pulpitis	1. Placebo acupuncture (14) Nonpiercing sham needles were used. 2. Real dipyrone (14) A 500 mg dipyrone tablet was administered. 3. Placebo dipyrone (14) A sham tablet without any active ingredient was administered.	Real acupuncture (14)	L14, ST44, CV23 and Yintang. The piercing needles made of stainless steel with a size of 30 mm × 0.25 mm were used for real acupuncture.	Acupuncturist	Pre and Post acupuncture	Acupuncture (0.02) was significantly more effective than dipyrone (0.09) in reducing pain (p < 0.041).
Murugesan (2017) [25]	Murugesan Irreversible (2017) pulpitis [25]	Sham acupuncture with a placebo tablet. Buprofen + sham acupuncture For sham acupuncture, patients received needle pricks at non-acupoints.	Classic acupuncture + placebo tablet.	LI4, ST6, ST7, SJ17. Special sterile, solid, silver needles were used for acupuncture.	Acupuncturist	15, 30, 45, and 60 minutes, and 12, 24, and 48 hours	The number of patients with pain was significantly less in the classic acupuncture group than in other groups ($p = 0.00$). Acupuncture (18.94 \pm 21.16 resulted in a significant pain reduction than sham acupuncture (57.83 \pm 5.53) and ibuprofen group (66.58 \pm 24.80).
Jalali (2015) [26]	Symptomatic irreversible pulpitis	Control (20) A cotton pellet and bandaid were used to stabilize the noncutting end of the sham needle.	Acupuncture (20)	L14 A disposable acupuncture needle of 25 mm in length and 0.25 mm diameter; was inserted 1–1.5 mm deep at the acupoint.	Acupuncturist	Assessed the success of IANB	The success of IANB was 60% in acupuncture and only 20% in the control group, which was statistically significant ($p < 0.05$).
Gross and Morse (1977) [3]	Irreversible pulpitis	1	Acupuncture (10)	LI4, GB7, GB44 The sterile stainless needle was inserted a few mm beneath the surface and manipulated for 25 minutes.	Acupuncturist	30 minutes	Complete analgesia was obtained only in one patient.

IANB = Inferior alveolar nerve block.



Table 3. Summary of acupoint selected in the included studies

Serial number	Acupoint	Location	Conditions
1	Hegu/LI-4	Highest point of the adductor pollicis muscle.	Facial pain and toothache
2	Neiting/ST44	Between second and third metatarsal joint.	Toothache, edema
3	Lianquan/CV23	Above hyoid bone	Facial pain
4	Yintang	Between eyebrows	Anxiety and pain
5	Jaiche/ST6	Angle of the mandible	Neuralgia and toothache
6	Xiaguan/ST7	Between mandibular notch and zygomatic arch	Facial pain, toothache and TMJ disorders
7	Yifeng/SJ17	Posterior to the ear lobule	Toothache, tinnitus and deafness.
8	GB7	Above auricle (in the hairline)	Modulating plasticity of central nervous system.
9	GB44	Between second and third toe	Chronic pain.

excluding these 11 patients, the remaining patients were asked to monitor their pain and record it at 12, 24, and 48 hours. It was reported that one patient in each SAP and SAI group were still suffering from pain after 24 h and so endodontic treatment was initiated. This meant that they were also excluded from the final analysis. The remaining patients in the CAP group that continued to feel pain was significantly lower than in the other two groups at all time points. In fact, none of the CAP group patients reported having severe pain after 48 hours compared to 8.3%, and 8.5% of patients in the SAP and SAI groups.

2. Postoperative pain

One study has evaluated the effect of acupuncture on postoperative pain after RCT in patients with a diagnosis of symptomatic apical periodontitis [20]. Subjects were randomized into two groups in equal proportion. In one group, real acupuncture was performed at the LI4 acupuncture point, while in another group, mock acupuncture was provided. Single visit RCT was performed 15 minutes after the acupuncture session in both groups. The acupuncture needle was removed after the completion of RCT. Patients were instructed to record their postoperative pain level using VAS until the 7th postoperative day. 400 mg of ibuprofen was prescribed to patients as rescue medication, and analgesic consumption of the patients was also monitored. A significant reduction in pain level in the acupuncture group compared to the placebo group was observed. For example, the value of the mean pain score was 0.07 and 21.93 on the 7th postoperative day in the acupuncture and placebo groups, respectively. Furthermore, analgesic consumption was significantly reduced in the acupuncture group.

3. Anesthetic success in patients with irreversible pulpitis

Only one randomized controlled trial has evaluated the

anesthetic success of acupuncture in patients with irreversible pulpitis [26]. In this randomized controlled trial, 40 patients with irreversible pulpitis in the mandibular molar were divided into two groups. In one group, acupuncture therapy was provided at LI4 point, while in the second group, sham acupuncture was administered. RCT was performed in both groups after administering an inferior alveolar nerve block (IANB). The additional requirement of supplemental anesthetic injection determined the success rate of the IANB. Results of this study revealed that 40% and 80% of patients required supplemental injection in the acupuncture and control groups, respectively, determining IANB to be significantly more successful in the acupuncture group.

4. Effect of acupuncture on pulpal anesthesia

So far, to our knowledge, only one study has evaluated the efficacy of acupuncture on pulp anesthesia [3]. Eight patients with ten teeth in need of endodontic treatment with vital pulp were included in this clinical study. Acupuncture was used as an initial analgesic measure. Six acupuncture points were used: LI4 on both hands, GB7 near a temporomandibular joint (TMJ) on either side, and GB44 on both feet. Out of ten, complete analgesia was achieved in one, while in 7 cases, partial analgesia was obtained, and in two cases, no analgesia was reported.

DISCUSSION

Acupuncture is used to treat common conditions from pain, nausea, and smoking cessation to more complex ailments like pulmonary diseases and stroke [2]. In addition, dentistry has also seen a significant increase in acupuncture and related therapies in the management of dental conditions like TMJ disorders and toothache [28]. In this review, we have evaluated the evidence gathered from the current literature on the efficacy of acupuncture on anesthetic success and pain reduction in patients undergoing non-surgical RCT.



Two studies have reported the use of acupuncture for emergency pain relief in endodontic patients. Both studies reported significantly better pain control with acupuncture than with sham acupuncture and an analgesic [24,25]. This finding is similar to the one reported by Grillo et al. [29] on the significant benefit of acupuncture in 120 patients waiting for emergency dental pain management. Based on the combined findings of these studies, acupuncture may be a beneficial treatment for emergency pain relief in conditions where AGPs are not possible, as in the present COVID-19 situation. COVID-19 has persisted as a major global health challenge since the World Health Organization first declared the pandemic in 2020 [22,27]. Several preventive measures have been suggested to halt its spread through preventing human-to-human contact, droplet or aerosol transmission. It is not surprising that it was suggested that aerosols generated during dental treatment could potentially lead to virus transmission [30]. Considering this, dental regulatory bodies have suggested minimizing such procedures. The use of medicines and non-AGPs or procedures with a minimal aerosol-generating potential like pulpotomy was advised instead of routine procedures like RCT to manage endodontic emergencies [31]. Acupuncture, with its proven efficacy in the management of pain as well as promising initial results in endodontic patients, may be employed as first-line emergency care for such patients where AGPs are not appropriate or available.

Postoperative pain after RCT has been reported in up to 40% of cases. The reasons attributed to this is the inflammation of the periapical tissues caused by mechanical, chemical, or biological injuries [32]. Clinicians continue to seek novel strategies to manage post-endodontic pain as it is a reasonably common sequela to endodontic treatment and current treatment options have unpredictable prognoses and may sometimes even fail to provide adequate pain relief. Considering this, a recent study [20] revealing that acupuncture minimizes postoperative pain in endodontic patients may be an interesting strategy to further explore, particularly as acupuncture is a largely safe with minimal side effects

Despite the benefits of acupuncture in pain management, the mechanism of its action remains unclear [20]. Gate control theory has been applied to explain the effects observed with acupuncture analgesia [33]. However, its inability to explain the entire range of analgesic effects and prolonged pain relief is the major limitation when trying to explain acupuncture analgesia with the proposed theory. It is suggested that acupuncture produces an analgesic effect by its action at local and central levels. The direct effect of acupuncture needles on the underlying nerves and associated structures is thought to underly the beneficial effects associated with it [34]. In

addition, it causes localized inflammation that triggers the release of neurotransmitters like bradykinin and histamine. These inflammatory mediators stimulate peripheral A-delta fibers that release enkephalin blocking painful sensations [35]. Further, A-delta fibers terminate in the raphe magnus nucleus in the midbrain, where serotonin is produced. Serotonin is an important neurotransmitter that plays a key role in amplifying the central effects of acupuncture by mediating anxiety and endocrinal functions [36]. It is also suggested that acupuncture may modify the N-methyl-D-aspartate (NMDA) receptor signaling pathway in the spinal cord leading to decreased pain perception by the patients [37]. The theory of acupuncture analgesia does however need to be verified in clinical studies involving patients with different endodontic conditions.

An IANB is deposited in the pterygomandibular space and is used to obtain anesthesia for procedures on mandibular teeth [38]. Despite being used most commonly in dentistry, it has a high failure rate ranging from 7% to 77% [39]. This failure is seen more when the pulp is inflamed, and various techniques and anesthetic agents have previously been used to alleviate this problem [16,40]. Premedication with antiinflammatory drugs has also been trialed with limited success [9]. Only one randomized controlled trial evaluated the effect of acupuncture on the success of IANB in patients with irreversible pulpitis [23]. A significantly higher success rate of nerve block was observed in patients who were administered acupuncture 15 minutes before anesthesia. This finding highlights higher chances of failure in up to 80% of nerve blocks in patients with irreversible pulpitis. Thus, showing how acupuncture may be more favorable as it minimizes those failures by 50%. Acupuncture may augment the anesthetic action of local anesthetic agents, particularly where the chances of their failure are high. Acupuncture has also been tested for obtaining pulp anesthesia in one study. This study reported 10% complete success and 70% partial success, further highlighting its positive and potential use [3]. It is important to add here that this study had some significant drawbacks such as small sample size, inconsistency in acupoint selection, use of six different acupoints including non-dental points in some patients, and a lack of control group, which may cause reporting bias [41]. Future studies should address these shortcomings and assess the role of acupuncture as an adjunct to local anesthetics in endodontic

Another useful application of acupuncture in endodontic patients could be the potential of it reducing anxiety surrounding the dental procedures. Dental anxiety is a common problem for the patient and the dentists [42] and is characterized by an exaggerated fear of dental procedures. Dental anxiety is known to adversely impact the patients'



quality of life and overall health [43]. Anxious patients also tend to experience a higher level of pain during and after RCT [44]. A recent cross-sectional study supports this theory as a greater incidence of pain in anxious patients was reported during RCT [45]. In addition, a randomized controlled trial showed that stimulation of Yintang acupoint resulted in a significant reduction of anxiety in patients planned for neurosurgical intervention [21]. The mechanism of acupuncture in causing decreased anxiety based on magnetic resonance imaging is related to reduced activity of the CNS components like the limbic system, amygdala, and hypothalamus [46]. Auricular acupuncture has been found to be effective in treating chronic anxiety disorder, and a similar anxiolytic effect was reported in studies related to dental anxiety [47,48]. The advantages of auricular acupuncture are demonstrated by its simple and easy to learn technique as well as a quick onset of treatment with minimal side effects [47]. In summary, acupuncture as treatment for the management of dental anxiety, although this may be compounded by generalized anxiety caused by the current COVID-19 pandemic [49], is safe and effective and could therefore prove beneficial when dealing with dental emergencies.

Despite the reported benefits of acupuncture in clinical studies, acupuncture is still viewed as the last treatment option [28]. The reason for this could be due to a combination of factors, such as needle phobias and time constraints that hinders the acceptance of treatment by patients. In addition, a lack of resources and formal training prevents its application by physicians and dentists [7]. Although acupuncture is an effective and safe therapy, cases of pneumothorax [50], cardiac complications (e.g endocarditis) [51], hepatitis [52] and even death [53] have been reported after acupuncture. The side effects reported in the literature are primarily due to a lack of due diligence on the part of non-qualified practitioners [50]. Strict aseptic conditions, the use of singleuse disposable needles, and application by trained medical practitioners can minimize the risk of such adverse effects [2]. It is also imperative to understand that acupuncture may not remove the source of endodontic pain but may provide a useful adjunct for pain relief [9]. Therefore, it may be particularly useful in cases where the traditional route of treatment may not be feasible because of various reasons such as contraindication of NSAIDs in patients with gastric ulcers [25].

A major limitation of this review is the small number of studies used to investigate the combined findings of the literature. Further limitations of the present review are caused by significant heterogeneity in terms of patient selection, acupuncture technique, and pain assessment in the included studies. These drawbacks may be attributed to the fact that acupuncture is a complex procedure [54]. Multiple factors

contribute to its complexity including inadequate sample size, randomizations, sham acupuncture, blinding, lack of adequate expertise and knowledge dissemination amongst western medical practitioners and absence of standard infection control measures may all affect its outcome [2,8]. Bias as a result of sham acupuncture and blinding is a major challenge for acupuncture studies [8] and was also observed in these studies on endodontic patients. The duration of pain assessment in the included studies was between 5 minutes and 7 days after acupuncture application. The acupoint selection in the included studies was not homogenous, and nine different acupoints were selected (Table 3). Similarly, the duration of acupressure application and type of acupuncture needle used varied with the different studies. However, the results of these studies do highlight the potential benefits of acupuncture as across all the studies, acupuncture reduced pain levels at all observed time intervals. This promising initial result should be precursor to more thorough clinical research using standardized techniques and a more homogenous study design.

CONCLUSIONS

Within the limitations of this review, it can be concluded that acupuncture is an effective alternative therapy for pain management that has provided an initial favorable response in endodontic patients. Thus, combined with restrictions on limiting AGPs like RCT during the ongoing COVID-19 pandemic, acupuncture may emerge as a promising firstline therapy for providing immediate pain relief and help to control dental anxiety. Unfortunately, there is a scarcity of good-quality clinical studies on acupuncture in the field of endodontics. Therefore, clinicians in future studies should address the heterogeneity related to the study methodology and other technical aspects related to acupuncture. What's more, future studies should adhere to the STRICTA guidelines while investigating acupuncture trials to improve reporting and subsequent interpretation and replication of these studies [55].

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CONFLICT OF INTEREST

The authors declare no conflict of interest.



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