An Integrative Review of Acupressure Interventions for Older people: A focus on sleep quality, depression, anxiety and agitation

Running title: Acupressure for older people

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Conflict of interest

The authors declare that they have no conflict of interest.

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Abstract

Objectives: This integrative review aimed to synthesize studies that investigated the effects of acupressure on sleep quality, depression, anxiety, and agitation in older people, and to describe the acupressure procedures and techniques applied in the included studies.

Methods: A literature search was conducted using electronic databases including CINAHL, Cochrane Library, EMBASE, and MEDLINE. The inclusion criteria for the review were studies examining the effect of acupressure in older people aged 60 years and above, measured the outcomes for sleep quality, depression, anxiety or agitation, applied body acupressure, and published in English language. The exclusion criteria were studies using auricular acupoints only, and articles published in any language other than English. Methodological quality of studies were assessed using the critical appraised tools developed by the Joanna Briggs Institute. The information about study design, findings and description of acupressure intervention were extracted, summarised and synthesized.

Results: A total of 255 articles were identified from the search and as well one article from cross-references. From there, a total of 19 studies were included in this review. Nine studies consistently showed positive effects of acupressure on sleep quality, and four studies consistently showed that acupressure reduced depression. The outcomes of acupressure on anxiety and agitation showed inconsistent findings, in which three studies measured anxiety and five studies measured agitation. There was also variation of acupressure techniques applied in the reviewed studies.

Conclusion: This review found some emerging evidences that acupressure can be beneficial for older people who suffer from sleep problems and depression. Use of specific acupressure points, with standardised acupressure treatment protocols, may improve sleep quality and possibly psychological wellbeing of older people. Future research with well-designed mixed method studies are required to produce stronger evidence, as well as in-depth understanding of acupressure intervention in aged care context.

Keywords: *acupressure, older people, sleep quality, depression, anxiety, agitation*

Key points

- Study findings consistently showed that acupressure improved sleep quality and reduced depression, but there were inconclusive findings for the effect of acupressure on anxiety and agitation.
- There were variations of the acupressure techniques applied in the reviewed studies, therefore it was inconclusive as to which acupressure method was the most effective.
- Well-designed studies, with standardized acupressure protocol on specific acupoints, are required to produce stronger evidence.
- A mixed method study including participants' view on benefits and limitations of acupressure intervention would provide a broader perspective of acupressure, the outcomes and related issues.

Introduction

The majority of older people are living with one or more chronic diseases,[1,2] this contributes to impaired physical functioning, poor quality of life and psychological distress.[2,3] As a consequence, older people are experiencing physical and psychological symptoms including sleep disturbance, depression, anxiety, agitation and many other symptoms.

Sleep disturbance is common in older adults because aging is associated with an increasing prevalence of comorbid health problems, side effects of prescribed medications, and psychosocial factors.[4] Insomnia and sleep disturbances often contributes to poor health status and quality of life, cognitive decline, impaired physical functioning, risk for falls and even mortality.[4,5] As well, poor sleep quality is closely related to depression and anxiety, and there is a bidirectional relationship between depression, anxiety and insomnia.[6,7]

Depression and anxiety are common in older people,[8] contributing to poor health, higher mortality rates, and increased healthcare costs.[9,10] Depression and anxiety also increases the risk of cognitive impairment and dementia,[11,12] as well, anxiety has been found to be associated with agitation in dementia.[13] Agitation that is prevalent in people with dementia increases caregivers' burden and distress.[14,15] Therefore, effective intervention strategies are required to manage common symptoms in older people. Use of complementary and alternative medicine (CAM) would be beneficial to older people who are affected by drug interactions and side effects of prescribed medications.[16,17]

Acupressure is one of the CAM modalities, which has a potential for promoting sleep quality[18-20] and psychological wellbeing.[21-23] Acupressure is the stimulation of acupuncture points (acupoints) using fingers, palms or devices. The purpose is to regulate and balance body energy (also known as *Qi*), maintain good health, and prevent illness.[24,25] Acupressure has been shown to have a role in reducing the stress response by altering hormone levels, neurotransmitter levels and its associated brain functioning.[21] Stimulation of acupoints regulates endorphins, serotonin, norepinephrine, adrenocorticotrophic hormone, cortisol, acetylcholine, and melatonin.[21,26] All of these hormones play major roles in sleep regulation and the functions of hypothalamic-pituitary-adrenal axis.[26] The regulation of neurotransmitters and hormonal factors depends on the locations of acupoints and techniques used.[26] Acupoint stimulation also regulates the autonomic nervous system by reducing sympathetic activities and increasing parasympathetic activity,[21,26] which can reduce the stress response and induce relaxation. Regulating autonomic nervous system, hormonal factors and neurotransmitters may have biological effects on inducing sleep, calmness and feelings of psychological wellness.

Systematic reviews evaluating the effects of acupressure on sleep quality in general population have shown promising results.[19,20] Other reviews evaluating the effects of acupressure on symptom management (fatigue, depression, anxiety, stress and agitation) concluded that evidence of acupressure effects on these symptoms was limited due to methodological quality and poor reporting.[18,27,28] There is lack of systematic reviews on effects of acupressure in older people. Therefore, we conducted a more comprehensive review of literature on the use of acupressure, specifically in older people.

Aim

This integrative review aimed to synthesize studies that investigated the effects of acupressure on sleep quality, depression, anxiety and agitation in older people, as well to describe the acupressure intervention procedures and techniques applied in the included studies.

Methods

Literature search and study selection

A literature search was conducted using electronic databases including CINAHL, Cochrane Library, EMBASE, and MEDLINE. Reference lists from the retrieved articles were manually searched. The search keywords used were *acupressure, sleep quality, insomnia, depression, anxiety, agitation, older people, elderly,* and *aged*. The inclusion criteria for the review were: 1) an original study examining the effect of acupressure in elderly or older people aged 60 years and above, 2) studies that measured any of the four outcomes namely: sleep quality, depression, anxiety or agitation, 3) body acupressure with manual application or using devices, and 4) articles published in English language.

This review evaluated methodology quality as well as acupressure interventions conducted in older people, therefore diverse types of study design: randomized controlled trial (RCT), experimental study, quasi-experimental or pre-and post-test design, and time serial design, were included. Studies using only auricular acupressure or acupoints in ears were excluded because underlying theory and mechanism of auricular points are different from body acupressure. Articles published in any language other than English were excluded due to language constraints. There was no limit for year of publication. According to the search outcome, this review included papers published from 1999 to the present.

Search outcomes

A total of 255 articles were identified from the electronic databases and one article from cross-references. From there, the titles and abstracts of articles were screened and assessed for eligibility. Thirty four full text articles were retrieved. Of these full text articles, 19 articles met the criteria and were included in the final review. There were two articles that reported the findings from the same study, conducted among patients with chronic obstructive pulmonary disease (COPD).[29,30] We included both articles because the first published article reported an anxiety outcome, and the second one reported a depression outcome. The flow PRISMA diagram is shown in Figure 1.[31]

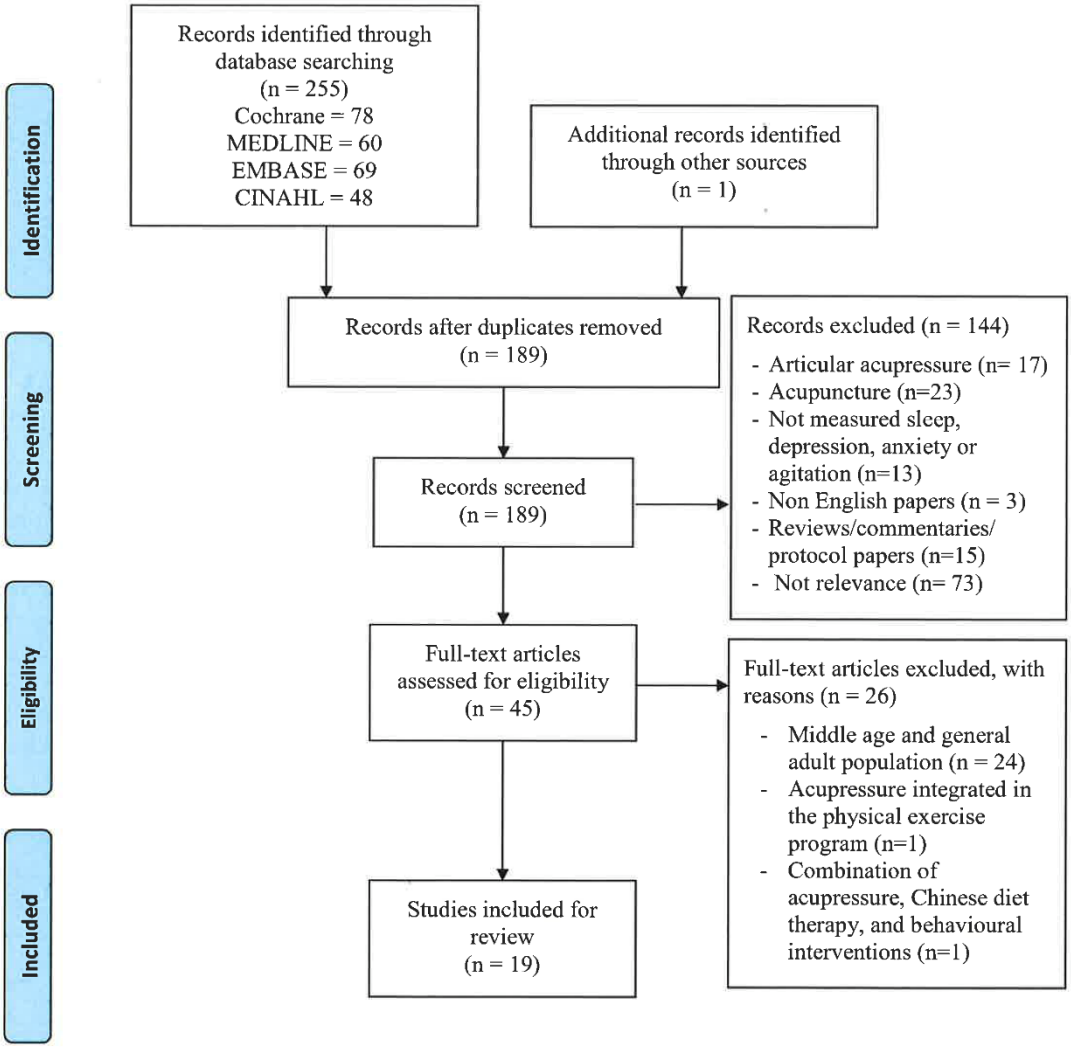

Figure 1 PRISMA flow diagram

Quality appraisal and data synthesis

Methodological quality of studies was assessed using critical appraisal tools developed by the Joanna Briggs Institute (JBI).[32] The JBI checklist for RCTs was used to assess RCTs, experimental, and cross-over design. The JBI checklist for non-randomized experimental studies was used to assess quasi-experimental studies, single group with pre-and post-test studies and time serial design.

We used narrative synthesis, instead of systematic review, due to heterogeneity of study designs and variation in acupressure intervention protocol. Narrative synthesis allows a better understanding of the results, methodological issues and intervention protocol. Information about study design, sample and setting, study groups, outcome measures, and results were extracted from the reviewed papers. Details of acupressure intervention: frequency and duration, selection of acupoints, procedures and techniques, were extracted and synthesized. The effects of acupressure on sleep quality, depression, anxiety and agitation were synthesized based on the findings and methodological quality of the studies.

Results

Characteristics of the studies

Of the 19 studies included, nine studies measured sleep outcomes.[33-41] four studies measured depression,[22,30,40,42] three studies measured anxiety,[23,29,39] and five studies measured agitation.[43-47] One study measured both sleep quality and depression,[40] and one other study measured sleep quality and anxiety.[39] There were eight RCTs and six randomized experimental studies, two quasi-experimental studies with a control group, two single-group studiee, and one time serial study. Two studies included qualitative interview after the intervention.[35,42] A summary of the studies included in this review is shown in Table 1.

As shown in Table 1, the various types of control and comparison groups were used. Three studies compared acupressure with sham acupressure and control groups,[35,36,47] and three studies compared with sham acupressure.[29,30,33] Eight studies compared acupressure with a control group receiving different types of care: routine care,[34] blood pressure measure,[22] massage and handholding,[23] light touch on acupoints,[37] sleep health instruction,[38] a wait listed control group,[40] guidance of mental health and education on sleep knowledge,[41] and regular care and visits.[42] One study compared acupressure with a different intervention, known as Montessor-based activity, and a control group.[44] Aroma-acupressure, aromatherapy

and control group were compared in one study.[45] One study compared eight groups, with different dosage of acupressure.[46] Two studies used a single-group.[39,43]

Outcome measurement tools

Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI) in eight studies, and one study used the Translated Athens Insomnia Scale (AIS-T). In addition to the PSQI, the Epworth Sleepiness Scale (ESS) was used in one study, a sleep log was used in one study, and an Actigraph was used in one study as an objective measurement of sleep. The PSQI is a reliable and valid tool to evaluate subjective sleep quality that is widely used in general population and older adults.[48-50] The AIS-T is a valid tool used to assess severity of insomnia in different populations, including older adults.[37,51,52] The ESS is used to assess subjective daytime sleepiness that is frequently used in research to evaluate the severity of excessive daytime sleepiness in older adults.[53,54] A sleep log is used to monitor daily sleep patterns with numeric rating scale ranging from 0-the worst to 10-sleep well.[36] Actigraph is an ambulatory device that measures objective sleep patterns; the device is equipped with a sensor, and is worn by participants to monitor and record gross motor activities continuously over extended period of time.[34]

Depression was measured using the Geriatric Depression Scale (GDS) in all four studies. The GDS is a reliable and valid tool designed specifically to measure self-rated depression in elderly.[55] For anxiety outcomes, two studies used the State-Trait-Anxiety Inventory (STAI) and one study used the Visual Analogue Scale (VAS). The STAI is a reliable self-reported scale for assessing anxiety in research and clinical practice.[56] The VAS for anxiety is a single-item rated on 100 mm vertical VAS anchored by ‘not at all’ and ‘worst possible’ at both extremes.[23]

The Cohen Mansfield Agitation Inventory (CMAI) was used to measured agitation in all five studies. The CMAI is an assessment tool used to monitor the frequency and intensity of agitation that has been shown to be reliable and valid.[57]

Methodological quality of the studies

In RCTs and experimental studies, all reported that randomization was used for participants’ assignment, but only eight studies reported the method of randomization and six studies did not report the randomization method leaving unclear information about true random

assignment. Allocation concealment was reported in three studies,[37,45,47] and the remaining studies did not report concealment. Ten studies reported participants in acupressure and comparison group were similar at the baseline level, three studies show differences at the baseline, and one study did not report clearly about baseline information.

Blinding of participants was present in three studies that compared acupressure with sham acupressure in two studies,[30,33] and control group receiving light touch in one study.[37] Two studies reported that participants were blinded for treatment allocation, but it was unclear because the researchers compared three groups: acupressure, sham acupressure and control group receiving routine care.[36,47] Therefore, the participants in the control group would be aware of their group allocation. Five studies did not blind the participants, and four studies did not report whether the participants were blinded for treatment allocation. Blinding of acupressure practitioners was applied in one study, in which trained interventionists were blinded for the nature of intervention and they did not know which protocol was therapeutic or sham.[47] The remaining studies did not blind the personnel who performed acupressure. Outcome assessors were blinded in eight studies, and six studies did not report on blinding of outcome assessors.

The completion rate of the acupressure intervention ranged from 82 -100% in 13 studies. One RCT had a 78.2% completion rate (79 out of 101), but the authors did not report the numbers that dropped-out from each group nor their reason for withdrawal.[40] Five studies reported that intention-to-treat (ITT) analysis was used, four studies did not apply ITT, and five studies were unclear about whether or not ITT analysis was applied. Quality appraisals for RCTs and experimental studies is shown in Table 2.

In five non-randomized trials, two studies had control group and three studies did not have a control group. Four studies had a completion rate of 96-100%, and one study had a very low completion rate of 57% (35 out of 20). Quality appraisal for non-randomized trials is shown in Table 3.

Acupressure interventions

Procedures and techniques

Application of acupressure procedures and techniques was varied across the studies. In sixteen studies, acupressure was performed by researchers, practitioners or trained assistants. Two studies employed self-acupressure performed by participants themselves who were

given training on acupressure techniques.[38,41] One study used the H7 insomnia control® device applied on the wrist overnight.[39] Summary of acupressure intervention applied in each study is shown in Table 4.

The majority of the studies used finger or thumb pressure. The procedure began with a massage or warm-up activities, followed by application of pressure on selected acupoints. The time of pressure applied on each acupoint ranged from 1-4 minutes; 3 minutes duration was the most common. Two studies applied finger pressure in circular or rotational movement.[33,34] Two studies used a light-strong-light pattern; pressure was gradually increased until it reached the optimal level, was sustained for 3 minutes, decreased gradually, and ended with a kneading.[46,47] In Yang et al.'s study,[45] each acupoint was pressed for two minutes with 2.5% lavender oil, followed by a warm up exercise for 5 minutes. The remaining studies used pressing or rubbing on each acupoint with figures or thumb.

Frequency and duration

The duration of acupressure session varied from 5-30 minutes, and 15-minute session was most common. The frequency of the acupressure sessions also varied: once daily, twice daily, four times daily, six times per week, five times per week, four times per week, three times per week, and two times per week. Total duration of the acupressure intervention varied from ten days to one year, and four-week duration was most frequently employed in eight studies.

Selection of acupoints

The most common acupoint used for sleep quality was *Shenmen* (HT7) in seven studies out of nine. Two studies used single acupoint on HT7,[37,39] and all the remaining studies use a combination of three or more different acupoints. Other commonly used acupoints for improving sleep quality were *Neiguan* (PC6) in five studies, *Amanian* in four studies, *Sanyinjiao* (SP6) in three studies, and *Yanquan* (KI1) in three studies.

The acupoints selected for agitation were similar in all five studies, using combination of *BaiHui* (GV20), *Fengchi* (GB20), *Shenmen* (HT7), *Neiguan* (PC6), and *Sanyinjiao* (SP6) in three studies. A combination of GV20, GB20, HT7 and PC6 with the *Yingtang* point was used in two studies. Acupoints selected for depression and anxiety were different in all studies, therefore common acupoints for depression and anxiety cannot be elicited from the studies included in this review.

Effect of acupressure on sleep quality

Nine studies included in this review (seven RCTs, one experimental, and one single-group studies) showed significant improvement of sleep quality after the acupressure intervention (Table 1).

Chen et al.,[35] conducted an experimental study in institutionalized elderly (N=84), comparing acupressure with a sham acupressure and a control groups. Acupressure was applied for 15 minutes, 5 days per week for 3 weeks, and the selected acupoints were HT7 in ears and hands, GV20, GB20, and Anmian. The sham acupressure was applied on non-acupoints, 1cm to 3 *cun* away from the meridian, and the control group received the conversation only. The *cun* is the unit of measurement based on the length and width of a certain part of the body. Three *cun* is the width of the four fingers when the index, middle, ring and little fingers are extended and closed together. The study findings indicated that sleep improvement in acupressure was significantly higher than in sham acupressure and control groups ($p < .001$). The use of sleep medications (the PSQI subscore) did not show a significant decrease in all three groups ($p = 1.19$). This study included a qualitative interview after acupressure, and participants expressed increased level of comfort and improved sleep quality.

In a RCT conducted by Reza et al.,[36] in elderly nursing home residents (N= 77), acupressure was compared with sham acupressure applied at 0.5 *cun* away from the meridian and the control group receiving routine care. Acupressure was applied at HT7 in ears and hands, PC6, KI1, SP6 in both legs, and Anmian, with a frequency of 3 times a weeks for 4 weeks. The duration of each acupressure session was not reported in this study. The results indicated that sleep quality in the acupressure group was improved significantly compared to the control group ($p < .001$), but the difference between acupressure and sham acupressure was unclear. The data for sleep medications did not show a significant difference between all three groups.

Lu et al.[34] conducted a RCT in psychogeriatric inpatients (N = 60), and compared acupressure with a control group receiving routine care. The selected acupoints were HT7, PC6, and KI1, applied for 9 minutes daily for 4 weeks. The findings indicated that sleep quality measured by the PSQI and actigraphy had improved more significantly in the acupressure group than the control group ($p < .001$). The frequency of using hypnotic drugs did not show a significant difference between the groups.

In a RCT conducted by Lai et al.[33] in nursing home residents (N = 62), acupressure was compared with a sham-controlled group receiving massage on non-acupoints. The intervention group received 24-minute acupressure, 3 times a week for 8 weeks, applied at BL10, CV14, KI1, DU20, and PC6. The findings indicated that participants in the acupressure group experienced improvement in sleep over time until four weeks after intervention ($p < .001$). The use of sleep medications was found to be reduced at the end of treatment and persisted until four weeks (p value was not reported).

Sun et al.,[37] conducted a RCT that compared acupressure with control group receiving light touch at the same acupoints, in long-term care residents (N = 50). The researchers used a single-acupoint (HT7) on both hands, applied for 5 minutes every nights before bedtime for 5 weeks. The results showed that acupressure at HT7 reduced insomnia during the intervention period and until two weeks after the intervention ($p < .001$). The data for use of sleep medications was not reported.

Chan et al.,[40] conducted a RCT that compared acupressure with a waiting list control group, in frail elderly living in community (N = 101). Acupressure sessions were conducted with 15-minute duration and a frequency of 4 times per week for 12 weeks, but the authors did not report the acupoints used. Sleep quality was measured as a secondary outcome that indicated a positive effect of acupressure on sleep quality ($p < .001$), and the data for use of sleep medications was not reported. The researchers measured the outcomes at post-treatment and 3 months post-treatment, however participants in control group received acupressure after post-treatment. This limited the comparison between acupressure and control at 3-month post-treatment follow up.

Zeng et al. [38] conducted a 1-year RCT in community living older adults (N = 82), using acupressure and control groups. The researcher had given training to the participants in acupressure groups to perform self-acupressure. The selected acupoints were PC6, HT7, SP6, and Anmian, applied for 30 minutes, 2 times daily for one year. Both acupressure and control groups received sleep health instructions, 3 sessions for 3 consecutive weeks, given by a community health staff. The sleep outcomes were measured at 3, 6, and 12 months. The findings indicated that sleep measures in acupressure group demonstrated more improvement over time than did control group ($p < .001$), and the data for use of sleep medications was not reported.

Lei, et al.,[41] conducted a RCT in elderly with primary hypertension (N = 68), comparing acupressure with a control group. The participants in the treatment groups performed self-acupressure 4 times daily for one month, and received guidance of mental

health and education on sleep knowledge once a week for 3 months. A nurse demonstrated and taught the method of massage on the selected acupoints; HT7, GB20, PC6, SP6, Anmian, and EX-HN 5. The control group received the same guidance of mental health and education of sleep knowledge, as given to the treatment group. The results indicated that sleep quality in acupressure group had improved significantly, compared to the control group ($p < .05$). The data for use of sleep medications was not reported.

Simoncini et al.,[39] conducted a single group study among institutionalized elderly with Alzheimer's disease (N = 129). The H7 insomnia control® device was applied on HT7 every evening before bedtime for 2 months. The results showed that sleep quality was significantly improved after the intervention ($p < .001$), until 4 months after the intervention ($p = .005$). The use of sedative drugs has been found to be reduced ($p < .001$). However, a single-group study without comparison group provided a low level of evidence.

Effect of acupressure on depression

Two RCTs and two quasi-experimental studies showed the positive effect of acupressure on depression. Wu et al.,[30] conducted an experimental study in patients with COPD (mean age = 73±9.7, N = 44), comparing true acupressure with sham acupressure. True acupressure was applied at GV14, CV22, B13, B23, L10, with 16-minute session, 5 times per week for 4 weeks. The sham acupressure was applied at SP5, SP3, and LI1 using the same frequency, duration and time frame applied in the true acupressure group. The results showed that depression was significantly reduced in true acupressure group compared to sham acupressure ($p < .001$). In a RCT conducted by Chan et al.,[40] depression was measured as a secondary outcome along with sleep quality. The findings indicated that acupressure, applied with 15-minute duration and a frequency of 4 times per week for 12 weeks, reduced depression ($p = .002$).

Tse and Au[42] conducted a quasi-experimental study among older adults with chronic knee pain (N=62), comparing acupressure with a control group. Acupressure group received 9-minute acupressure twice a week for 4 weeks, applied at ST35, ST6 and Medial Xiyan (EX-LE5) in both knees. The control group received the regular care and visits each week, but the authors did not report details about the visits. The results indicated that the acupressure group had a significant decrease in depression level, compared to the control group ($p = .027$). Their study included qualitative interview regarding participants'

experience of the acupressure program, and the participants expressed feeling of pleasure, pain relief, and increased physical activity.

Sok[22] conducted a quasi-experimental study with older women living alone (N = 76), comparing acupressure with a control group. The experimental group received acupressure applied on the Joktaeyang Bangkwang Kyeong (the meridian points in the vessels of *qi*, half of the body surface), 15-minute duration twice a week for 8 weeks. For the control group, only blood pressure was measured, but the author did not report details about this. The study findings indicated that the depression level decreased significantly in the acupressure group ($p < .001$).

Effect of acupressure on anxiety

Two experimental studies conducted in patients with COPD showed positive effects of acupressure on anxiety, and a single-group study conducted in elderly people with Alzheimer's disease showed no significant positive effect of acupressure on anxiety.

Tsay et al.[23] conducted an experimental study in patients with COPD who were receiving mechanical ventilation (aged ≥ 60, N = 52). The experimental group received 15-minute acupressure every day for 10 days, applied at PC6 and LI4 on both hands, and HT7 on both ears. The control group received massage and handholding, but the authors did not describe the frequency and duration. The results indicated that the level of anxiety in acupressure group was significantly lower compared to control group ($p = .011$). Similarly, Wu et al.[29] conducted an experimental study in patients with COPD, and found anxiety be reduced more significantly than that of sham acupressure ($p < .001$). The study characteristics and intervention procedures were the same as that reported in Wu et al.[30]

In Simoncini et al.'s study,[39] using the H7 insomnia control® device, anxiety was measured along with sleep quality and other outcomes related to Alzheimer's disease. Study findings indicated a positive trend of improvement in anxiety, but there was not a significant different from the baseline anxiety level.

Effect of acupressure on agitation

Studies investigating the effect of acupressure on agitation, among institutionalized elderly with dementia, showed conflicting results. Four studies reported the positive effect of acupressure on agitation, but one study found no significant result.

Yang, et al.,[43] employed a single group receiving both an acupressure and a control treatment. First, participants received 15-minute acupressure twice daily, 5 days a week for 4 weeks, applied at GV20, GB20, HT7, PC6, and SP6. The data were collected before and after the acupressure intervention. After one week post-intervention, the same participants received a control treatment, in which the researcher visited to the participants and talked to them (visiting and conversation) for 15 minutes daily over 4 weeks. Data were collected before and after the control treatment, and these data were compared with the first data collected before and after acupressure intervention. The results indicated that acupressure reduced agitation ($p < .001$). However, a single group being employed as intervention and control group, and very low completion rate (20 out of 31) limited the validity of the results.

Lin et al.[44] used a cross-over design (N = 133), comparing three treatment groups: acupressure, Montessori-based activities, and a presence group (conversation with participants). The acupressure session was 15-minute duration given 6 days per week for 4 weeks, applied at GV20, GB20, HT7, PC6, and SP6. The results indicated that acupressure and the Montessori-based activities significantly decreased agitation compared to presence group ($p = .001$, $p < .001$). The author did not report the difference between acupressure and the Montessori-based activities.

Yang et al.[45] conducted an experimental study (N = 186), comparing aroma-acupressure with aromatherapy and control group receiving routine care. The aroma-acupressure was applied with 2.5% lavender oil for 15 minutes, 5 days per week for 4 weeks, at GV20, GB20, HT7, PC6, and SP6. The results indicated that aroma-acupressure and aromatherapy significantly decreased agitation compared to the control group ($p < .001$, $p = .01$), and aroma-acupressure had greater effect than aromatherapy on agitation.

Kwan et al.[46] conducted a pilot study with time serial design (N = 24), which included eight dosage combination groups (shown in Table 1). Agitation was measured every week until four weeks after the end of the intervention. The selected acupoints were *Yingtang*, GV20, GB20, HT7, and PC6. The effect of acupressure on agitation onset was seen immediately at week 1 ($p < .001$), resurged at week 4, and was sustained until week 6 ($p < .001$). The optimal dosage appeared to be a course of twice a day for 2 weeks. In this pilot study, a small sample size (n=24) with too few participants in each group (n=3), no random allocation and no control group limited the validity of the results.

In a recent RCT conducted by Kwan et al.,[47] acupressure was compared with sham acupressure using non-acupoints and control group receiving usual care (N = 119). Acupressure was applied at *Yingtang*, GV20, GB20, HT7, and PC6 for 10 minutes twice

daily, 5 days per week for 2 weeks. Agitation was measured at baseline (T0) and in the 3rd (T1), 5th (T2), and 8th (T3) weeks post intervention. The findings indicated a downward trend in agitation over time in the acupressure group, but it failed to reach a significant level (p = .052). This RCT used similar acupressure technique, acupoints, as well as measurement tool (CMAI) applied in the earlier studies. It showed insignificant effect of acupressure on agitation, contradicting with the other study findings.

Discussion

This integrative review evaluated acupressure interventions conducted among older people, with focus on sleep quality, depression, anxiety and agitation. Study findings consistently showed that acupressure improved sleep quality. Sleep improvement in acupressure group was sustained until 2-4 weeks after intervention.[33,37] The findings also indicated that level of depression was reduced after acupressure the intervention, but follow-up outcomes were not measured after post-test assessment.[22,30,40,42] There were inconsistent findings on the effects of acupressure on anxiety and agitation. The results were inconclusive due to heterogeneity of the study designs and variation in acupressure interventions.

Quality of studies and methodological issues

In quality appraisal of RCTs and experimental studies, only two RCTs were good quality,[37,47] according to the JBI checklist. The remaining studies had limitations which included the absence of blinding participants, personal and outcome assessment, differences in participants' baseline characteristics between groups, and failure to apply ITT analysis. In non-randomized controlled studies, two quasi-experimental studies have good quality,[22,42] and the remaining studies had low quality due to absence of a control group and high drop-out rates. Beside study limitations, inadequate reporting precluded the accurate assessment of the study quality. Therefore, reporting of studies should include details of research design, procedures, and acupressure techniques, so that the readers can assess methodological quality and replicability of the study.[18,20]

In most of the reviewed studies, researchers performed manual acupressure therefore blinding of patients and personnel was not possible. The nature of acupressure intervention involves personal contact with practitioners and study participants, therefore blinding of patients and personnel is challenging. Some studies used sham acupressure or light touch on acupoint for blinding participants.[30,33,36,37,47] In Kwan et al.'s study,[47] trained interventionists

were blinded for the nature of intervention and they did not know which protocol was therapeutic or sham. In consideration of the sham protocol, cautious identification of the location for sham acupressure is important to maintain a satisfactory blinding as well as to minimize potential therapeutic effects.[58]

In this review, the majority of the studies measured quantitative outcome data, limiting in-depth understanding of participants' views on acupressure. Only two studies included qualitative interview, and reported briefly about the positive experience of participants.[42,35] A mixed method study, including participants' view on benefits and limitations of acupressure, would provide a broader picture of interventions, the outcomes and related issues.[18]

Acupressure techniques and acupoints selection

There were variations of the acupressure techniques applied in the reviewed studies. It was inconclusive as to which acupressure method was the most effective. Overall, 15-minute acupressure session and 4-week duration was commonly used. Some acupressure studies commenced treatment sessions with 3-5 minutes massage or warm-up activities, followed by application of finger or thumb pressure on the selected acupoints.[23,29,30,33,35,38,41,43,44] The combination of massage with acupressure might have an impact on the outcomes. Future studies should apply only finger or thumb pressure without including massage, to ascertain the effect of acupressure on the outcome variables.

In traditional acupressure practice, firm pressure using thumb or fingers to stimulate the acupoints is the most fundamental technique.[59,60] The amount of pressure depends on the location of the acupoint and the thickness of the skin, muscle and fatty tissue at the point.[61,62] In addition, the intensity of pressure should be adjusted according to the level of tolerance of the individual patient.[24,63]

In the reviewed studies, the most common acupoint used to improve sleep was HT7 and other common points were PC6, SP6, KI1, and Anmain (known as extra point). Common acupoints used for agitation in dementia were GV20, GB20, HT7, PC6, and SP6. Acupoints selected for depression and anxiety were varied in the included studies. In TCM, the acupoints have different treatment functions when used in different conditions,[64] therefore selection of the acupoints is based on the actions of specific acupoint and the patient's condition. A combination of two or more different acupoints is frequently used to enhance treatment efficacy.[64,65] In sleep deprivation, acupressure application on common acupoints;

HT7, PC6 and SP6 that regulate internal organ functioning, may enhance efficacy of acupressure to improve sleep quality. In addition, the Anmian and KI1 were occasionally used acupoints to promote sleep.[64] In future studies, standardization of acupressure protocol with focus on specific acupoints would provide strong body of evidence that can be incorporated in practice settings.

Implications for future research

Acupressure is non-invasive technique that is simple and easy to learn. This review found acupressure has the potential to improve sleep quality and psychological wellbeing. Acupressure applied manually using finger pressure is less likely to incur adverse effects. Nurses, caregivers, family members, and even patients themselves can learn this simple technique of acupressure.[24,25] Integration of acupressure in care of older persons would promote their sleep quality and wellbeing. This could further reduce the costs and side effects of conventional medication treatment. However, a stronger level of evidence on efficacy of acupressure is needed. Further research with well-designed trials are required to provide more conclusive evidence in the use of acupressure in promoting sleep quality.

In future research, random assignment of participants should be employed to ensure each participants has the equal chance of receiving treatment protocol,[66] and the randomization procedure should be described in detail in study report. When blinding of patients and personnel is not possible, allocation concealment and blinding of outcome assessors is recommended to avoid selection bias and detection bias.[67] Data analysis should use intention-to-treat method that includes all randomized participants in the groups to which they were randomly assigned, regardless of withdrawal from the study or deviation from the protocol.[68] Furthermore, the majority of the studies were conducted in Asian countries, and only one study was in Italy.[39] Studies on acupressure should be replicated and expanded in western populations, to determine the feasibility and effects of acupressure in a different cultural context.

This review has identified limitations such as excluding non-English papers due to language constraint, therefore methodological issues and details of acupressure intervention used in those non-English papers could not be assessed. Also, the studies with poor quality were included in this review which may limit clear and definitive conclusions.

Conclusion

This review found emerging evidences to support the effectiveness of acupressure interventions for older people who suffer from a combination of insomnia, depression and anxiety. Acupressure could be a useful strategy to address these conditions. Use of specific acupressure points, with standardised acupressure treatment protocol, may improve sleep quality and possibly the psychological wellbeing of older people. Future research with well-designed mixed method studies are required to produce stronger evidence for clinical decision making, as well as in-depth understanding of acupressure intervention in an aged care context.

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Table 1 Summary characteristics of the studies

No.	Author/ Country	Setting & Sample	Study design	Study groups (number analysed in each group)	Outcome measures	Results
1.	Chen et al.[35] Taiwan	Institutionalised residents from public living-assisted facility. Recruited; 102 Completed; 84	Randomized block experimental	i. Acupressure (n=28) ii. Sham acupressure: non-acupoint, 1cm-3cun away from meridian (n=28) iii. Control: conversation (n=28)	PSQI	A > S/C ($p < .001$)
2.	Reza et al.[36] Iran	Elderly in nursing home Recruited; 90 Completed; 77	RCT	i. Acupressure (n=25) ii. Sham acupressure; 0.5 *cun* away from meridian (n=26) iii. Control; routine care (n=26)	PSQI Sleep log	*PSQI:* A> C ($p < .001$) S = C ($p = .078$) *Sleep log:* A > C ($p = .003$) A = S ($p = .318$)
3.	Sun et al.[37] Taiwan	Residents in long-term care facilities Recruited; 50 Completed; 44	RCT	i. Acupressure (n=25) ii. Control (n=25); light touch on same acupoints	AIS-T	A > C ($p < .001$)
4.	Lu et al.[34] Taiwan	Psycho-geriatric inpatients from psychiatric hospital Recruited; 63 Completed; 60	RCT	i. Acupressure (n=30) ii. Control; routine care (n=30)	PSQI Actigraphy	*PSQI :* A > C ($p < .001$) *Actigraph:* A > C ($p < .001$)
5.	Lei et al.[41] China	Elderly patients with primary hypertension; inpatients in elderly ward Recruited; 68	RCT	i. Acupressure and guidance of mental health education of sleep knowledge (n=34) ii. Control; guidance of mental health education of sleep knowledge (n=34)	PSQI	A > C ($p < .05$)

6.	Simoncini et al.[39] Italy	Institutionalized patients with Alzheimer's disease Recruited; 129	NR (single group, pre-and post-test)	i. Acupressure (n=129)	PSQI, STAI	*PSQI:* Significantly improved after intervention ($p < .001$), until 4 months after intervention ($p = .005$) *STAI:* NS
7.	Zeng et al.[38] China	Older adults living in community (age ≥ 60) Recruited; 90 Completed; 82	1-Year RCT	i. Acupressure training and sleep health instructions (n=42) ii. Control; sleep health instruction (n=40)	PSQI EES	*PSQI & EES:* A > C ($p < .001$)
8.	Lai et al.[33] Taiwan	Residents living in nursing home. Recruited; 62	RCT	i. Acupressure (n=31) ii. Sham-Controlled; massage on non-acupoint (n =31)	PSQI	A > S ($p < .001$)
9.	Chan et al.[40] Hong Kong	Frail elderly living in community Recruited; 101 Completed; 79	RCT	i. Acupressure (n=50) ii. Control; waiting list (n=51)	PSQI GDS	*PSQI:* A > C ($p < .001$) *GDS:* A > C ($p = .002$)
10.	*Wu et al.[30] Taiwan	Patient with COPD (mean age 73 ± 9.7) Recruited; =44	Randomized block experimental	i. Acupressure (n=22) ii. Sham acupressure (n=22)	GDS	A > S ($p < .001$)
11.	Tse & Au[42] Hong Kong	Older persons with chronic knee pain Recruited; 62 Completed; 62	Quasi-experimental with control group	i. Acupressure (n = 32) ii. Control; regular care and visit each week (n = 30)	GDS	A > C ($p < .027$)
12.	Sok[22] Korea	Older women living alone Recruited; 76 Completed; 76	Quasi-experimental with control group	i. Acupressure (n=38) ii. Control group (n=38)	GDS	A > C ($p < .001$)

13.	*Wu et al.[29] Taiwan	Patient with COPD (mean age 73 ± 9.7) Recruited; 44	Randomized block experimental	i. Acupressure (n=22) ii. Sham acupressure (n=22)	STAI	A > S ($p < .001$)
14.	Tsay et al.[23] Taiwan	Patients with COPD (aged ≥ 60) Recruited; 52 Completed; 52	Randomized block experimental	i. Acupressure (n=26) ii. Control; massage and handholding (n=26)	VAS-anxiety	A > C ($p = .011$)
15.	Yang et al.[43] Taiwan	Nursing home residents with dementia Recruited; 31 Completed; 20	Single group pilot study	i. Single group receiving both acupressure and control treatment	CMAI	A > C ($p < .001$)
16.	Lin et al.[44] Taiwan	Institutionalized residents with dementia Recruited; 133	Cross-over design	i. Acupressure ii. Montessori-based activity (MBA) iii. Control (present)	CMAI	A & MBA > C ($p = .001$& $p < .001$)
17.	Yang et al.[45] Taiwan	Institutionalized patients with dementia Recruited; 186	Experimental	i. Aroma-acupressure (n=56) ii. Aroma therapy (n=73) iii. Control; routine care (n=57)	CMAI	AA > AT > C ($p < .001$, $p = .01$)
18.	Kwan et al.[46] Hong Kong	Institutionalized residents with dementia Recruited; 25 Completed; 24	Pilot study, Time serial design with eight dosage-combination groups	i. twice daily for 1 week ii. twice daily for 2 weeks iii. twice daily for 3 weeks iv. twice daily for 4 weeks v. once daily for 1 week vi. once daily for 2 weeks vii. once daily for 3 weeks viii. once daily for 4 weeks	CMAI	Effect of acupressure on agitation onset was seen at week 1 ($p < .001$), sustained until week 6 ($p < .001$). The largest effect was twice a day for 2 weeks.

19.	Kwan et al.[47] Hong Kong	Nursing home residents with Dementia Recruited; 119	RCT	i. Acupressure (n=39) ii. Sham acupressure; using non-acupoints (n=41) iii. Control; usual care (n=39)	CMAI	NS (p = .052)

RCT; Randomized Controlled Trial, A; Acupressure, C; Control, S; Sham acupressure, AA; Aroma-acupressure, AT; Aromatherapy, PSQI; Pittsburgh Sleep Quality Index, AIS-T; Translated Athens Insomnia Scale, STAI; State-Trait Anxiety Inventory, EES; Epworth Sleepiness Scale, GDS; Geriatric Depression Scale, VAS; Visual Analogue Scale, CMAI; Cohen Mansfield Agitation Inventory, NR; Not reported, NS; Not significant.
*Publication on the same study.

Table 2 Quality appraisal for RCTs and experimental studies

JBI Checklist	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Score
Chen et al.[35]	Y	U	Y	U	N	U	Y	Y	N	Y	Y	Y	Y	8
Reza et al.[36]	U[1]	U	Y	U[2]	N	Y	Y	Y	N	Y	Y	Y	Y	8
Sun et al.[37]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	12
Lu et al.[34]	Y	U	Y	N	N	U	Y	Y	N	Y	Y	Y	Y	8
Lei et al.[41]	Y	U	Y	N	N	U	Y	Y	U	Y	U	Y	Y	7
Zeng et al.[38]	Y	U	Y	N	N	Y	Y	Y	N	Y	Y	Y	Y	9
Lai et al.[33]	U[1]	U	N	Y	N	Y	Y	Y	Y	Y	U	Y	Y	8
Chan et al.[40]	Y	U	N	N	N	U	Y	N	Y[3]	Y	U	Y	N	5
Wu et al.[30]	U[1]	U	U	Y	N	Y	Y	Y	U	Y	U	Y	Y	7
Wu et al.[29]	U[1]	U	Y	U	N	U	Y	Y	U	Y	U	Y	Y	6
Tsay et al.[23]	U[1]	U	Y	U	N	Y	Y	Y	U	Y	Y	Y	Y	8
Lin et al.[44]	U[1]	U	Y	N	N	Y	Y	Y	U	Y	Y	Y	Y	8
Yang et al.[45]	Y	Y	N	U	U	U	Y	Y	Y	Y	U	Y	Y	8
Kwan et al.[47]	Y	Y	Y	U[2]	Y	Y	Y	Y	Y[4]	Y	Y	Y	Y	12

Y; Yes, N; No, U; Unclear, the authors did not report clearly

[1] Reported randomized allocation, but randomization method was not clearly reported.
[2] Reported that participants were blinded, but participants in control group who received routine care would be aware of their allocation
[3] Intention to treat analysis was used for pre-and post-test data, not for post 3 months follow up.
[4] Used modified intention to treat analysis; all subjects were included after randomization except those withdrawn before undergoing the first session of intervention.

Table 3 Quality appraisal for non-randomized and quasi-experimental studies

JBI Checklist	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Score
Simoncini et al.[39]	Y	Y	NA	N	Y	Y	NA	U	U	4
Tse & Au [42]	Y	Y	Y	Y	Y	Y	Y	U	Y	8
Sok[22]	Y	Y	Y	Y	Y	Y	Y	U	Y	8
Yang et al.[43]	Y	Y	N	N	Y	N	NA	Y	Y	5
Kwan et al.[46]	Y	U	NA	N	Y	Y	Y	Y	Y	6

Y; Yes, N; No, U; Unclear, NA; Not Applicable

Table 4. Summary of acupressure interventions

	Author Country	Acupoints used	Acupressure procedure & technique	Acupressure performer	Intervention sessions & duration	Follow-up
1.	Chen et al.[35] Taiwan	HT7 in ears and hands, GV20, GB20, and Anmian in head.	15-mins session; 5 mins finger massage and 10 mins acupoint pressure with 2 mins/point, between 1pm and 10pm. The correctness of acupressure was confirmed if the participants felt sore, numb, distended, and/or warm. Detailed technique of acupressure application was not reported.	Principal investigator completed 10-week basic training	5days/week for 3 weeks	At the end of intervention
2.	Reza et al.[36] Iran	HT7 in ears and hands, PC6, KI1, SP6 in both legs, and Anmian in head.	The precision of acupoint was confirmed if the participants felt sore, heavy, numb, distended, and/or warm Detailed technique of acupressure application was not reported.	Main investigator trained by expert	3 times/week for 4 weeks	At the end of intervention
3.	Sun et al.[37] Taiwan	HT7 in both wrists	Acupressure was applied before bed time with the interval of five- second pressure followed by one second rest, with 5 mins total duration.	Trained assistants	Every night before bedtime for 5 weeks.	Every week during intervention until 2 weeks after end of intervention
4.	Lu et al.[34] Taiwan	HT7, PC6 , KI1	9-min session; 3 mins per point: The pressure was applied to the acupoints using ventral part of the fingers (thumb, index and middle fingers) at 90 degree angle. Massage the area around the point in a circular fashion at a rate of 2-3 rotation per second.	Chinese medicine nurse specialist	Daily between 7-9pm for 4 weeks	At the end of intervention

5.	Lei et al.[41] China	HT7, GB20, PC6, SP6, Anmian, EX-HN 5	Nurse demonstrated and taught patients massage method: Massage face: Gently massage from the middle of the face to the backwards by hands. An-pressing and Rou-kneading manipulations on Anmian and GB20 by finger pulps of forefingers. An-pressing and Rou-kneading manipulations at both EX-HN 5 by thumbs, and circular Gua-scraping the two orbits by both forefingers. Dian-digital pressing and An-pressing manipulations at HT7 by fingertips of forefingers, each time lasted for 1-2 secs, then repeat on bilateral GB20 by bilateral thumbs, PC6 and SP6.	Self-acupressure trained by a nurse	4 times daily for 1 month	At the end of intervention
6.	Simoncini et al.[39] Italy	HT7	The H7 Insomnia control® device was applied every evening 30 mins before sleep, and removed on the following morning.	Nursing staff applied the device	Every night for 2 months	T1; At the end of intervention, T2; 4 months after end of intervention
7.	Zeng et al.[38] China	PC6, HT7, SP6 and Anmian	Participants performed acupressure exercises at home for at least two 30-min sessions daily. Researcher demonstrated acupressure techniques; 90-mins training session once a week over three weeks. To massage the face with both hands: rubbing the hands, placing the middle fingers near the nose, moving up beside the nose to the brow and the forehead, and then moving from the front of the ear back to the nose area, using	Self-acupressure trained by researcher	1 year	3, 6, and 12 months of intervention

			gentle, even, coordinated movements and a consistent speed. Press the Anmian acupoint with middle finger pad. Rub the PC6, massage was clockwise with thumb. Press the HT7 with thumb. Rub the SP6 with thumb. The precision of acupressure was confirmed if participants felt sore, numb, heavy, distended, or warm.			
8.	Lai et al.[33] Taiwan	BL10, CV14, KI1, DU20, PC6	24-min session (3 mins initial massage and 21 mins acupressure): Apply consistent finger-tip pressure of 3-5 kg with rotational movement. The interval of pressure on each point was 5 secs followed by 1 sec rest for 3 mins. Precision of selected acupoints was confirmed if the participants felt sore, numb, distended, warm at the point of application.	Specialists received 42-hour training on the concepts and techniques of acupressure	3 times/week for 8 weeks, given at night time	T1; At the end of intervention, T2; 4 weeks after end of intervention
9.	Chan et al.[40] Hong Kong	NR	15-min acupressure Detailed technique of acupressure application is not reported.	Chinese medicine practitioner and trained care givers	4 times/week for 12 weeks	T1; At the end of intervention, T2; 3 months after end of intervention
10.	Wu et al.[30] Taiwan	GV14, CV22, B13, B23, L10	16-minute session: Effleurage neck and shoulder for 4 mins. Press and rub GV14 for 3 mins, Press the CV22 for 1-5 mins, Press and rub the B13 for 3 mins, Press and rub B23 for 1.5 mins Press and rub the L10 for 3 mins.	Investigator	5 times/week for 4 weeks	At the end of intervention

11.	Tse &Au[42] Hong Kong	ST35, ST36 and Medial Xiyan (EX-LE5) in both knees	9 mins for each knee: 6 cycles in total; 15-sec pressure and 15-sec rest for each point, and repeat. Patient position; lying on bed with knee flex to 30 degrees. Researchers' arm and thumb forming a vertical line on the knee, using 5 pound force of pressure.	Researchers and assistants	Twice/week for 4 weeks	At the end of intervention
12.	Sok[22] Korea	In Joktaeyang Bangkwang Kyeong in *Qi* flow.	15-min finger acupressure pressing on the Joktaeyang Bangkwang Kyeong in qi flow; half of the total body surface, at the convenient time of the day. Participants wore thin clothing and assumed prone position on a blanket.	Researchers and assistants	Twice/week, for 8 weeks.	At the end of intervention
13.	Wu et al.[29] Taiwan	GV14, CV22, B13, B23, L10	16-min session: 1. Effleurage: hold, rub and press the neck and each shoulder for 4 mins 2. Press and rub GV14 for 3 mins 3. Press the CV22 for 1-5 mins 4. Press and rub the B13 for 3 mins, both sides at the same time. 5. Press and rub B23 for 1.5 mins, both sides at the same time. 6. Press and rub the L10 for 3 mins. Points 2-6 were pressed or rubbed once/sec for 5 secs, then released for 1 sec.	Investigator	5 times/week for 4 weeks	At the end of intervention
14.	Tsay et al.[23] Taiwan	PC6, LI4 on both hands, HT7 on ears	15-min session; 3 mins massage on shoulder and both arms and 12 mins acupoint massage with 4 mins/point. Detailed technique of acupressure application was not reported.	TCM nurse therapist	Every day for 10 days at mid-afternoon.	Daily during intervention until 7 days after intervention

15.	Yang et al.[43] Taiwan	GV20, GB20, HT7, PC6, SP6	15-min session; pressure was applied to each acupoint for two minutes, after 5 mins of warm-up activity. Pressure was applied using thumb, the index, middle and ring fingers.	Principal investigator received Chinese medicine and acupressure training	Twice daily, 5 days/week for 4 weeks	One week after end of intervention
16.	Lin et al.[44] Taiwan	GB20, DU20, HT7, PC6, SP6	15-min session: Begin with 5-min of warm-up activities, holding, rubbing, and pressing the palms and finger joints. After the warm-up, acupressure was applied using finger pressure to each acupoint for 2 mins.	Research assistants	6 days/week, for 4 weeks	At the end of each intervention period
17.	Yang et al.[45] Taiwan	GV20, GB20, HT7, PC6, SP6	*Aroma-acupressure:* Each acupoint was pressed 2 mins with 2.5% lavender oil, followed by a warm up exercise for 5 mins, total duration not longer than 15 mins.	NR	Once daily, 5 days/week for 4 weeks	At the end of intervention, 3 weeks after end of intervention
18.	Kwan et al.[46] Hong Kong	*Yingtang* GV-20, GB-20, HT-7, PC-6,	9-min session: Acupressure application followed a light-strong-light pattern. Pressure was gradually increased until it reached the optimal level, was sustained for 3 minutes, decreased gradually, and ended with a kneading. The optimal pressure was defined as the level when *Deqi* sensations (i.e., soreness, numbness, distention, heaviness). *Yingtang* was first pressed for 3 mins. GV20 and GB2 were then pressed simultaneously for 3 mins. Finally, PC6 and HT7 were pressed simultaneously for 3 mins.	NR	Once and twice a day for four durations (1, 2, 3, and 4 weeks) formed eight dosage combinations	Weekly until 4 weeks after intervention

19.	Kwan et al.[47] Hong Kong	*Yingtang* GV20, GB20, HT7, PC6,	10-minute session: First, *Yingtang* was pressed for 3 mins, Then, GV20 and GB20 were pressed simultaneously for 3 mins, Finally, HT7 and PC6 were pressed simultaneously for 3 mins. Acupressure application followed a light-strong-light pattern. The optimal pressure was defined as the level when *Deqi* sensations (i.e., soreness, numbness, distention, heaviness).	Trained assistants	2 sessions per day, 5 days a week for 2 weeks	T1; At the end of intervention, T2; 3 weeks after end of intervention T3; 6 weeks after end of intervention

TCM; Traditional Chinese Medicine, NR; Not reported