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Effectiveness and safety of moxibustion treatment for nonspecific lower back pain: protocol for a systematic review

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Complete List of Authors:	<p>Leem, Jungtae; Kyung Hee University, Department of Clinical Korean Medicine</p> <p>Lee, Seunghoon; Kyung Hee University Korean Medicine Hospital, Dept. of Acupuncture & Moxibustion Medicine</p> <p>Park, Yeon Cheol; Kyung Hee University Hospital at Gangdong, Acupuncture & Moxibustion</p> <p>Seo, Byung-Kwan; Kyung Hee University Hospital at Gangdong, Acupuncture & Moxibustion</p> <p>Cho, Yeeun; Kyung Hee University Korean Medicine Hospital, Dept. of Acupuncture & Moxibustion Medicine</p> <p>Kang, Jung Won; Kyung Hee University, Acupuncture & Moxibustion Medicine</p> <p>Lee, Yoon Jae; Jaseng Medical Foundation, Jaseng Spine and Joint Research Institute</p> <p>Ha, In-Hyuk; Jaseng Medical Foundation, Jaseng Spine and Joint Research Institute</p> <p>Lee, Hyun- jong ; Daegu Oriental hospital of Daegu Haany University, Department of Acupuncture & Moxibustion medicine</p> <p>Kim, Eun-jung; Dongguk University, Dept. of Acupuncture & Moxibustion, College of Oriental Medicin</p> <p>Lee, Sanghoon; Kyung Hee University, Dept. of Acupuncture & Moxibustion, College of Korean Medicine; Kyung Hee University, Dept. of Clinical Korean Medicine, Graduate School</p> <p>Nam, Dongwoo; Kyung Hee University, Department of Acupuncture & Moxibustion</p>
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Manuscripts

1 **Effectiveness and safety of moxibustion treatment**
2 **for nonspecific lower back pain: protocol for a**
3 **systematic review**

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5 Jungtae Leem^{1,2}, Seunghoon Lee³, Yeoncheol Park⁴, Byungkwan Seo^{4,5}, Yeeun Cho³,
6 Jungwon Kang^{3,5}, Yoonjae Lee⁶, In-Hyuk Ha⁶, Hyun-jong Lee⁷, Eun-jung Kim⁸, Sanghoon
7 Lee^{1,3,5}, and Dongwoo Nam^{3,5*}

8
9 ¹Department of Clinical Korean Medicine, Graduate School, Kyung Hee University, 26
10 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea

11 ²Korean Medicine Clinical Trial Center, Kyung Hee University Korean Medicine Hospital,
12 23 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea

13 ³Department of Acupuncture & Moxibustion Medicine, Kyung Hee University Korean
14 Medicine Hospital, 23 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea

15 ⁴Department of Acupuncture & Moxibustion, Kyung Hee University Hospital at Gangdong,
16 892 Dongnam-ro, Gangdong-gu, Seoul, 05278, South Korea.

17 ⁵Department of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee
18 University, 26 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea.

19 ⁶Jaseng Spine and Joint Research Institute, Jaseng Medical Foundation, 858 Eonju-ro,
20 Gangnam-gu, Seoul, 06017, South Korea.

21 ⁷Department of Acupuncture & Moxibustion, College of Korean Medicine, Daegu Haany
22 University, Haanydaero 1, Gyeongsan-si, Gyeongsangbuk-do, 38610, South Korea.

23 ⁸Department of Acupuncture & Moxibustion, College of Oriental Medicine, Dongguk

1
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4 24 University, 268 Buljeong-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, 13601, South Korea
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26 ***Correspondence to**

27 Dongwoo Nam, KMD, PhD

28 Department. of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee

29 University, 26 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea

30 Telephone: + 82-2-958-9207, Fax: + 82-2-958-8169, E-mail: hanisanam@daum.net

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4 31 **ABSTRACT**

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6 32 **Introduction:** Purpose of this study protocol for a systematic review is to evaluate the
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8 33 effectiveness and safety of moxibustion treatment for nonspecific lower back pain patients.

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10 34 **Methods and Analysis:** We will conduct an electronic search of several databases from their
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12 35 inception to November 2016, including EMBASE (OVID), MEDLINE (PubMed), Cochrane
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14 36 Central Register of Controlled Trials (CENTRAL), Allied and Complementary Medicine
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16 37 Database (AMED), Wanfang Database, Chongqing VIP Chinese Science and Technology
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18 38 Periodical Database (VIP), China National Knowledge Infrastructure Database (CNKI),
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20 39 Korean Medical Database (KMBASE), Korean Studies Information Service System (KISS),
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22 40 National Discovery for Science Leaders (NDSL), Oriental Medicine Advanced Searching
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24 41 Integrated System (OASIS), the Korea Institute of Science and Technology (KISTI), and
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26 42 KoreaMed. Randomized controlled trials investigating any type of moxibustion treatment
27
28 43 will be included. The primary outcome will be pain intensity and functional status/disability
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30 44 due to lower back pain. The secondary outcome will be a global measurement of recovery or
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32 45 improvement, work-related outcomes, radiographic improvement of structure, quality of life,
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34 46 and adverse events (presence or absence). The Cochrane risk of bias tool will be used to
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36 47 evaluate methodological quality. Risk ratio or mean differences with a 95% confidence
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38 48 interval will be used to show the effect of moxibustion therapy when a meta-analysis is
39
40 49 available.

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42 50 **Ethics and Dissemination:** This review will be published in a peer-reviewed journal and will
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44 51 be presented at an international academic conference for dissemination. Our results will
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46 52 provide current evidence of the effectiveness and safety of moxibustion treatment in
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48 53 nonspecific lower back pain patients, and thus will be beneficial to patients, practitioners, and
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50 54 policy makers.
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4 56 **Trial registration number:** CRD42016047468 in PROSPERO 2016
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For peer review only

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4 57 **Strengths and limitations of the present study protocol**

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6 58 • Our review provides a systematic, objective, and comprehensive evaluation of the
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8 59 effectiveness and safety of moxibustion treatment in patients with lower back pain
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10 60 that is nonspecific.
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13 61 • Our review and meta-analysis provide new and useful information for practitioners,
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15 62 policymakers, and patients.
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18 63 • Various treatments with moxibustion and clinical outcomes reviewed in our study will
19
20 64 help to design clinical trial studies of moxibustion treatment for nonspecific lower
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22 65 back pain.
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25 66 • Chinese and Korean databases were searched to avoid a language bias.
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28 67 • The major limitation of our study protocol is that some of the reviewed trials have
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30 68 small sample sizes; this limitation affects our objective and comprehensive
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32 69 assessment of the risks and benefits of moxibustion treatment for nonspecific lower
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34 70 back pain.
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71 INTRODUCTION

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73 More than 70% of people suffer from lower back pain in developed countries[1].
74 Approximately 90% of back pain is nonspecific[2], indicating that most people the
75 pathophysiological origin of the back pain cannot be specified[1]. Moreover, specifying and
76 treating the factor that contributes to lower back pain is difficult because several co-related
77 factors are involved, including psychological, work-related, and other individual factors[3].
78 Most of acute back pain is spontaneously relieved, but 20% of acute back pain patients suffer
79 from chronic or persistent lower back pain[4]. The widely accepted definition of chronic
80 lower back pain is a pain that persists for more than three months[5]. Even though
81 conventional treatments such as medication or surgery have shown some efficacy against
82 lower back pain[6,7], many lower back pain patients are dissatisfied with conventional
83 treatment[8].

84 The proportion of patient using complementary and alternative medicine to treat lower back
85 is increasing[9]. Acupuncture plays an important role in Traditional East Asian Medicine
86 (TEAM) treatment of pain[10]. Several systematic reviews on the effectiveness and safety of
87 acupuncture treatment in lower back pain patients have been published[11–14]. Moxibustion
88 is an important treatment modality in TEAM treatment that stimulates acupoints with the heat
89 energy of a burning herbal preparation[10,15]. Absorption of the therapeutically active
90 components of the herbal preparation also contributes to the effect of moxibustion[15]. In
91 TEAM theory, moxibustion treatment promotes qi stimulation and resolves qi stagnation at
92 an acupoint[15]. Two types of moxibustion, direct moxibustion and indirect moxibustion, are
93 widely used in TEAM treatment. Systematic reviews have been published about the
94 effectiveness of moxibustion on several disease, including insomnia, hypertension, irritable
95 bowel syndrome, and constipation[16–19]. We conducted a preliminary search of several
96 Chinese, English, and Korean databases for publications within the last 5 years (2011-2016)

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4 97 that included randomized clinical trial data on moxibustion treatment in patients with
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6 98 nonspecific back pain; the results of this search revealed more than 300 articles. We excluded
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9 99 several articles, including animal studies, reviews, and studies of moxibustion treatment for
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11 100 specific back pain due to a specific pathology such as lumbar disc herniation. Ultimately, our
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13 101 preliminary search identified 15 relevant articles to include in our planned review[20–34].
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15 102 A systematic review summarizes the evidence of relevant current clinical trial studies; this
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17 103 effort provides supportive information for the design of future clinical trial studies. A
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19 104 systematic review of studies on the effectiveness of Traditional Chinese Medicine (TCM)
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21 105 treatment of back pain was published in 2015[1]. This review of TCM treatment for lower
22
23 106 back pain deals with studies involving acupuncture, acupressure, moxibustion, cupping, Gua
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25 107 Sha, qigong, herbal medicine, and tuina treatments. A focus on moxibustion treatment was
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27 108 beyond the scope of that review, as, no article on moxibustion treatment for back pain was
28
29 109 included finally. Thus, the range of interventions that are explored in that previous review is
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31 110 too broad to clarify the critical factors related to moxibustion treatment of lower back pain
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33 111 that are of interest to practitioners and researchers; such factors include the treatment duration,
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35 112 position, intensity, frequency, species of moxa, various outcome parameters, and side effects
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37 113 of moxibustion treatment.
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41 114 A systematic review of studies on the effectiveness of heat sensitive moxibustion treatment
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43 115 for a lumbar disc herniation has also been published[20]. However, as the prevalence of
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45 116 lower back pain that is secondary to a lumbar disc herniation (LDH) is low, it is not our target
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47 117 condition. Only 3 to 4 percent of patients with lower back pain who came to a primary clinic
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49 118 suffered from spinal stenosis or a lumbar disc herniation[35]. An underlying specific
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51 119 pathology usually cannot be identified in patients with nonspecific back pain[36]. Moreover,
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53 120 many patients with nonspecific back pain also suffer from musculoskeletal pain[37].
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55 121 Furthermore, L5 and S1 spinal nerve root damage due to disc protrusion or degenerative
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4 122 changes in the vertebrae are common causes of lower back pain in patients with a lumbar disc
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6 123 herniation[38].
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9 124 Our preliminary search found clinical studies with various experimental designs, for
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11 125 example, moxibustion versus usual care or conventional treatment, moxibustion versus
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13 126 another TCM intervention such as (electro) acupuncture, and moxibustion adjuvant therapy
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15 127 with acupuncture, among others. Thus, it may be prudent to conduct a systematic review of
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17 128 the clinical trial studies involving various types of moxibustion treatments for nonspecific
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19 129 lower back pain that includes clinical outcomes. Nonetheless, we anticipate that our study
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21 130 will overcome the limitations of previous systematic reviews of studies involving lower back
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23 131 pain and TCM [1,20].
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26 132 To our knowledge, a systematic review that focuses on the effectiveness of various types of
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28 133 moxibustion treatment for nonspecific lower back pain and includes Chinese and Korean
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30 134 studies has not been published. Thus, we propose to conduct a systematic review that focuses
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32 135 on the effectiveness and safety of moxibustion treatment in patients with nonspecific lower
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34 136 back pain. We will summarize the current evidence and provide useful information to
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36 137 practitioners, patients, and policymakers. A summary of the current evidence from
37
38 138 moxibustion clinical trial studies of lower back pain will benefit the development of future
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40 139 moxibustion clinical trial protocols. In the present article, we describe our methods and plan
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42 140 for a systematic review.
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48 142 **Objectives**

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52 143 The objective of the present review is to systematically evaluate the effectiveness and safety
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54 144 of moxibustion treatment of nonspecific lower back pain.
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4 146 **METHODS**

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6 147 **Study registration**

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8 148 The systematic review protocol registration number in the International Prospective Register
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10 149 of Systematic Reviews (PROSPERO) is CRD42016047468. This systematic review protocol
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12 150 complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
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14 151 Protocols (PRISMA-P) statement guidelines[39,40]. In addition, our review will be
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16 152 conducted in compliance with the Preferred Reporting Items for Systematic Reviews and
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18 153 Meta-Analyses (PRISMA) statement guidelines[41].
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24 155 **Criteria for study inclusion**

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26 156 Type of studies

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28 157 We will include only randomized controlled trials (RCT) in this review.
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33 159 Type of participants

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35 160 Patients diagnosed with only nonspecific lower back pain will be included in the review.

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37 161 Trials studies of lower back pain due to other pathologies such as lumbar disc herniation,

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39 162 fibromyalgia, tumor, compression fracture, infection, trauma, cauda equine syndrome,

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41 163 vertebral canal stenosis, scoliosis, or ankylosing spondylitis will be excluded. There will be

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43 164 no restriction of sex, age, ethnicity, disease duration, or disease severity.
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48 166 Type of interventions

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50 167 Moxibustion therapy will be compared to a placebo control, conventional treatment, no

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52 168 treatment, and an unproven control treatment. Moxibustion adjunctive therapy in combination

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54 169 with conventional treatment will be compared to conventional treatment alone. Any type of

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56 170 moxibustion will be included, regardless of the treatment frequency, duration, material, type,
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4 171 and method. Studies involving direct moxibustion, indirect moxibustion, warm needling,
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6 172 moxa-burner moxibustion, heat sensitive moxibustion, natural moxibustion, herbal patching,
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8 173 and crude drug moxibustion will also be included. Research that compared different
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10 174 moxibustion materials, doses, or durations of moxibustion treatment will not be included.
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12 175 Studies that evaluated the effect of moxibustion with at least 1 day of follow-up will be
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14 176 included.
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22 179 *Primary outcomes.* Pain intensity and functional status/disability will be a primary outcome.
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24 180 Pain intensity will be evaluated using the visual analogue scale (VAS)[42] or the numerical
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26 181 rating scale (NRS)[43]. Functional status/disability will be evaluated using validated
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28 182 measurement tools such as the Roland Morris Disability Questionnaire (RMDQ) or the
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30 183 Oswestry Disability Scale[44,45].
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35 185 *Secondary outcome.* The secondary outcomes will include the following: 1) global
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37 186 measurements of recovery or improvement, such as subjective symptom improvement, the
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39 187 proportion of responders, overall improvement, and perceived recovery; 2) work-related
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41 188 outcomes, such as productivity, return to work status, and the number of absent days for work;
42
43 189 3) radiographic improvement of structure; 4) quality of life measurements using validated
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45 190 tools such as the Short Form Survey Instrument (SF-36) [46] and Euroqol-5D (EQ-5D) [47];
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47 191 and 5) complications and adverse events
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52 193 **Search Methods**

53 194 Electronic search

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55 195 We will conduct an electronic search of several databases from their inception to December
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4 196 2016. Four English databases will be searched, namely, EMBASE (OVID), MEDLINE
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6 197 (PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Allied
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8 198 and Complementary Medicine Database (AMED); three Chinese database will be searched,
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10 199 namely, the Wanfang Database, the Chongqing VIP Chinese Science and Technology
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12 200 Periodical Database (VIP), and China National Knowledge Infrastructure Database (CNKI);
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14 201 and six Korean databases will be searched, namely, the Korean Medical Database
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16 202 (KMBASE), the Korean Studies Information Service System (KISS), National Discovery for
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18 203 Science Leaders (NDSL), the Oriental Medicine Advanced Searching Integrated System
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20 204 (OASIS), Korea Institute of Science and Technology (KISTI), and KoreaMed. The search
21
22 205 term will be composed of two parts, moxibustion (e.g., moxibustion or moxabustion or moxa
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24 206 or artemisia or mugwort) and back pain (e.g., lower back pain, sciatica, radiculopathy,
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26 207 lumbago, backache, back pain, or lumbo-sacral). The online Supplementary Appendix 1
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28 208 present our detailed search strategy that will be specific to MEDLINE (PubMed).
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34 210 Searching other resources

35 211 PROSPERO, the International Clinical Trials Registry Platform (ICTRP), and
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37 212 ClinicalTrials.gov will also be searched to identify systematic reviews or ongoing/completed
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39 213 clinical trials. We will conduct a hand search of relevant journals and their conference
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41 214 proceeding. Thesis and bibliographic references of included trials will also be reviewed.
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47 216 **Analysis**

48 217 Study selection

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50 218 Two review authors (J Leem and Y Cho) will independently screen titles and abstracts in
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52 219 retrieved article lists from independent electronic and hand searches to exclude any obviously
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54 220 irrelevant articles. The full text of the remaining articles will be downloaded to assess their
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221 eligibility for inclusion in our review according to predefined criteria. Disagreement between
222 these two authors will be resolved by discussion. If these authors do not reach an agreement,
223 a third review author (D Nam) will make the final decision.

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225 Data extraction and management

226 Two review authors (J Leem and Y Cho) will read all included articles and extract data
227 according to a predefined data sheet that includes the publication year, author, title, journal,
228 country, hospital setting, study design, allocation concealment, randomization method,
229 blinding, participants number, dropout number, intervention of treatment and control groups,
230 treatment frequency and number, diagnostic criteria, disease duration, disease severity,
231 outcome and results, and adverse event. Disagreement between these two authors will be
232 resolved by discussion. If these authors do not reach an agreement, a third review author (D
233 Nam) will make the final decision. We will request via e-mail that the corresponding author
234 of the original study send data when the results are ambiguous.

235

236 Assessment of reporting quality and risk of bias

237 Two review authors (J Leem and Y Cho) will independently assess the risk of bias according
238 to the Cochrane risk of bias tool[48] outlined in the Cochrane Handbook for Systematic
239 Reviews for Intervention[49]. Risk of bias assessment categories will include the following:
240 (1) allocation concealment; (2) random sequence generation; (3) blinding of outcome
241 assessors; (4) blinding of participants; (5) incomplete outcome data; (6) selective outcome
242 reporting; and (7) other biases. The level of the risk of bias will be evaluated as either a low,
243 high, or unclear risk of bias. Disagreement between these two authors will be resolved by
244 discussion. If these authors do not reach an agreement, a third review author (D Nam) will
245 make the final decision.

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6 247 Unit of analysis

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8 248 If studies measure the same outcome repeatedly, we will perform an analysis according to a
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10 249 timeline definition. Immediate follow-up will mean up to one week after the last intervention.
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12 250 Short-term follow-up will mean from one week to three months. Intermediate-term follow-up
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14 251 will mean from three months to 1 year after the last treatment. Long-term follow-up will
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16 252 mean more than 1 year after the last treatment.
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21 254 Measures of a treatment effect

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23 255 For dichotomous data, a risk ratio (RR) and the 95% confidence (CI) interval will be used to
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25 256 estimate a treatment effect. For continuous data, the mean difference (MD) and the 95% CI
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27 257 will be used to estimate a treatment effect when the same outcome scale or method is used.
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29 258 Standardized mean difference (SMD) and the 95% CI will be used to estimate a treatment
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31 259 effect when a different outcome scale or method is used.
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37 261 Managing missing data

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39 262 We will contact the corresponding author of an article via e-mail to obtain any missing data.
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41 263 If there is no response to an e-mail, we will exclude the data from our analysis, and describe
42
43 264 the reason and impact of this exclusion in the Discussion section.
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48 266 Assessment of a reporting bias

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50 267 Publication bias will be assessed visually using funnel plot asymmetry if more than 10
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52 268 articles are included[49]. An Egger's regression test will be used to quantitatively evaluate
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54 269 funnel plot asymmetry[50].
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4 271 Assessment of heterogeneity
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6 272 The heterogeneity of included studies will be quantitatively evaluated using an I^2 statistic that
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8 273 is derived from a chi-square test. The I^2 statistic will be interpreted according to the following
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10 274 criteria: 1) 75-100% will indicate considerable heterogeneity; 2) 50-90% will indicate
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12 275 substantial heterogeneity; 3) 30-60% will indicate moderate heterogeneity; 4) 0-40% will
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14 276 indicate little to no heterogeneity. In this manner, an I^2 statistic of more than 50% will
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16 277 indicate the presence of substantial heterogeneity for the included studies[51]. If the I^2
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18 278 statistic is more than 75%, a meta-analysis will not be conducted[52]. Instead, we will
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20 279 qualitatively describe the effectiveness and safety of moxibustion treatment.
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26 281 **Data synthesis**

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28 282 The Review manager (REVMAN) software for Windows will be used to perform a meta-
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30 283 analysis and to calculate the risk ratio or (standardized) mean difference (Version 5.3;
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32 284 Copenhagen; The Nordic Cochrane Center, The Cochrane Collaboration, 2014). We will
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34 285 adopt a random effect model when the I^2 statistic is more than 50%, otherwise we will adopt
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36 286 a fixed effect model in a meta-analysis.
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40 287 41 288 **Subgroup analysis**

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43 289 To identify heterogeneity between the included studies, a subgroup analysis will be
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45 290 conducted if there is sufficient number of articles in each subgroup. The criteria of a
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47 291 subgroup analysis will be as follows: 1) disease duration, such as chronic (more than 3
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49 292 months) or acute lower back pain; 2) type of control group, such as placebo moxibustion,
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51 293 conventional treatment, other TCM treatment, and no treatment; 3) type of moxibustion, such
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53 294 as direct moxibustion, indirect moxibustion, warm needling moxibustion, moxa burner
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55 295 moxibustion, heat sensitive moxibustion, and crude drug moxibustion; 4) species of herb used
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4 296 in the moxibustion treatment; and 5) treatment number, frequency, and duration.
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297 298 **Sensitivity analysis**

299 If there are a sufficient number of included articles, a sensitivity analysis will be carried out
300 after removing low quality articles to identify the robustness of a result. The methodological
301 quality will be assessed according to the STandards for Reporting Interventions in Clinical
302 Trials of Acupuncture (STRICTA) checklist[53]. After excluding low quality articles, we will
303 conduct a second meta-analysis. The results and effect size of the two meta-analyses will be
304 compared and discussed.

305 306 **DISCUSSION**

307 The purpose of this proposed systematic review and meta-analysis will be to evaluate the
308 effectiveness and safety of moxibustion treatment of nonspecific lower back pain. When
309 compared to acupuncture research, the quantity and quality of moxibustion therapy research
310 is relatively low. The STandards for Reporting Interventions in Clinical Trials of Moxibustion
311 (STRICTOM) was published in Chinese in 2013[54], but has not been widely adopted and
312 translated into English. A recent systematic review was published on TCM treatment of lower
313 back pain[1]. This review included a variety of interventions that are practiced in TCM, such
314 as acupuncture, moxibustion, herbal medicine, cupping, and manual therapy, among others.
315 However, the various interventions that were included in that review have too broad of a
316 range to appropriately evaluate the issues that are specific to moxibustion treatment of lower
317 back pain. Moreover, it did not include any trial studies of moxibustion treatment. A
318 systematic review has also been published regarding the effectiveness of heat sensitive
319 moxibustion for lumbar disc herniation[20]. However, this review is not concerned with
320 nonspecific back pain, but rather, lower back pain that is secondary to lumbar disc herniation.

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4 321 Therefore, the protocol described here is for the first systematic review and meta-analysis on
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6 322 the effectiveness and safety of any type of moxibustion treatment in nonspecific lower back
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8 323 pain patients. We anticipate that our review and meta-analysis will provide useful information
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10 324 to practitioners, policymakers, and patients.
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17 327 REFERENCES

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474 **AUTHORS' CONTRIBUTIONS**

475 Dongwoo Nam conceived of the study. The protocol was drafted by Jungtae Leem and Yeeun
476 Cho. The search strategy was developed by Seunghoon Lee and Sanghoon Lee. The inclusion
477 criteria were developed by Yeoncheol Parka and Byungkwan Seo. The authors Jungwon
478 Kang and Eun-jung Kim revised the manuscript. The authors Yoonjae Lee, In-Hyuk Ha, and
479 Hyun-jong Lee developed the analysis plan. Jungtae Leem submitted the manuscript for
480 publication. All authors have read and approved the final manuscript.

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486 **COMPETING INTERESTS**

487 The authors declare no competing interests.

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489 **PROVENANCE AND PEER REVIEW**

490 Not commissioned; externally peer reviewed.

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Appendix 1 : MEDLINE(Pubmed) Search Strategy

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6 #1 Low Back Pain/
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8 #2 Sciatica/
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10 #3 Radiculopathy/
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12 #4 (lumbar OR lumbosacral OR lumbo-sacral OR back) adj5 (pain* OR ache* OR
13
14 aching) [TIAB]
15
16 #5 backache*[TIAB] OR lumbago[TIAB] OR sciatica[TIAB]
17
18 #6 radiculopathy[TIAB] OR radiculitis[TIAB] OR radicular pain*[TIAB]
19
20 #7 (nerve root* adj5 (pain* OR avulsion OR compress* OR disorder* OR pinch* OR
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22 inflam* OR imping* OR irritat* OR entrap* OR trap*)) [TIAB]
23
24 #8 {or #6-#7}
25
26 #9 back*[TIAB] OR lumbosacral[TIAB] OR lumbo-sacral[TIAB] OR lumbar[TIAB]
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28 #10 #8 and #9
29
30 #11 {or #1-#5, #10}
31
32 #12 Moxibustion/
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34 #13 Artemisia/
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36 #14 (moxibustion or moxabustion or moxa or artemisia or mugwort\$.tw.
37
38 #15 {or #12-#14}
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40 #16 #10 and #15
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42 #17 randomized controlled trial [PT]
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44 #18 controlled clinical trial [PT]
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46 #19 randomized [TIAB]
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50 #21 clinical trials as topic [mesh: noexp]
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52 #22 randomly [TIAB]
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4 #23 trial [TI]
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8 #25 animals [mh] NOT humans [mh]
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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input type="checkbox"/>		1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			Not update for previous review
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input type="checkbox"/>		56
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input type="checkbox"/>		5-30
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input type="checkbox"/>		475-479
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments			Not amendment for previous review
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input type="checkbox"/>		480-483
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>		480-483
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol			No roles exist
INTRODUCTION					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Rationale	6	Describe the rationale for the review in the context of what is already known	<input type="checkbox"/>		95-140
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input type="checkbox"/>		155-191
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input type="checkbox"/>		155-191
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input type="checkbox"/>		194-214
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input type="checkbox"/>		194-214
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input type="checkbox"/>		225-234
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input type="checkbox"/>		218-223
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input type="checkbox"/>		225-234
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input type="checkbox"/>		225-234
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input type="checkbox"/>		179-191
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input type="checkbox"/>		236-245
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>		281-286
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of	<input type="checkbox"/>		271-286

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		consistency (e.g., I^2 , Kendall's tau)			
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input type="checkbox"/>		288-304
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>		271-286
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input type="checkbox"/>		261-269
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)		<input type="checkbox"/>	Not Applicable

Peer review only



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

BMJ Open

Effectiveness and safety of moxibustion treatment for nonspecific lower back pain: protocol for a systematic review

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014936.R1
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Complete List of Authors:	<p>Leem, Jungtae; Kyung Hee University, Department of Clinical Korean Medicine Lee, Seunghoon; Kyung Hee University Korean Medicine Hospital, Dept. of Acupuncture & Moxibustion Medicine Park, Yeon Cheol; Kyung Hee University Hospital at Gangdong, Acupuncture & Moxibustion Seo, Byung-Kwan; Kyung Hee University Hospital at Gangdong, Acupuncture & Moxibustion Cho, Yeeun; Kyung Hee University Korean Medicine Hospital, Dept. of Acupuncture & Moxibustion Medicine Kang, Jung Won; Kyung Hee University, Acupuncture & Moxibustion Medicine Lee, Yoon Jae; Jaseng Medical Foundation, Jaseng Spine and Joint Research Institute Ha, In-Hyuk; Jaseng Medical Foundation, Jaseng Spine and Joint Research Institute Lee, Hyun- jong ; Daegu Oriental hospital of Daegu Haany University, Department of Acupuncture & Moxibustion medicine Kim, Eun-jung; Dongguk University, Dept. of Acupuncture & Moxibustion, College of Oriental Medicin Lee, Sanghoon; Kyung Hee University, Dept. of Acupuncture & Moxibustion, College of Korean Medicine; Kyung Hee University, Dept. of Clinical Korean Medicine, Graduate School Nam, Dongwoo; Kyung Hee University, Department of Acupuncture & Moxibustion</p>
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For peer review only

1 **Effectiveness and safety of moxibustion treatment**
2 **for nonspecific lower back pain: protocol for a**
3 **systematic review**

4
5 Jungtae Leem^{1,2}, Seunghoon Lee³, Yeoncheol Park⁴, Byungkwan Seo^{4,5}, Yeeun Cho³,
6 Jungwon Kang^{3,5}, Yoonjae Lee⁶, In-Hyuk Ha⁶, Hyun-jong Lee⁷, Eun-jung Kim⁸, Sanghoon
7 Lee^{1,3,5}, and Dongwoo Nam^{3,5*}

8
9 ¹Department of Clinical Korean Medicine, Graduate School, Kyung Hee University, 26
10 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea

11 ²Korean Medicine Clinical Trial Center, Kyung Hee University Korean Medicine Hospital,
12 23 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea

13 ³Department of Acupuncture & Moxibustion Medicine, Kyung Hee University Korean
14 Medicine Hospital, 23 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea

15 ⁴Department of Acupuncture & Moxibustion, Kyung Hee University Hospital at Gangdong,
16 892 Dongnam-ro, Gangdong-gu, Seoul, 05278, South Korea.

17 ⁵Department of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee
18 University, 26 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea.

19 ⁶Jaseng Spine and Joint Research Institute, Jaseng Medical Foundation, 858 Eonju-ro,
20 Gangnam-gu, Seoul, 06017, South Korea.

21 ⁷Department of Acupuncture & Moxibustion, College of Korean Medicine, Daegu Haany
22 University, Haanydaero 1, Gyeongsan-si, Gyeongsangbuk-do, 38610, South Korea.

23 ⁸Department of Acupuncture & Moxibustion, College of Oriental Medicine, Dongguk

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24 University, 268 Buljeong-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, 13601, South Korea

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26 ***Correspondence to**

27 Dongwoo Nam, KMD, PhD

28 Department. of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee

29 University, 26 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea

30 Telephone: + 82-2-958-9207, Fax: + 82-2-958-8169, E-mail: hanisanam@daum.net

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4 31 **ABSTRACT**

5
6 32 **Introduction:** Purpose of this study protocol for a systematic review is to evaluate the
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8 33 effectiveness and safety of moxibustion treatment for nonspecific lower back pain patients.

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10 34 **Methods and Analysis:** We will conduct an electronic search of several databases from their
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12 35 inception to December 2016, including EMBASE (OVID), MEDLINE (PubMed), Cochrane
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14 36 Central Register of Controlled Trials (CENTRAL), Allied and Complementary Medicine
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16 37 Database (AMED), Wanfang Database, Chongqing VIP Chinese Science and Technology
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18 38 Periodical Database (VIP), China National Knowledge Infrastructure Database (CNKI),
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20 39 Korean Medical Database (KMBASE), Korean Studies Information Service System (KISS),
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22 40 National Discovery for Science Leaders (NDSL), Oriental Medicine Advanced Searching
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24 41 Integrated System (OASIS), the Korea Institute of Science and Technology (KISTI), and
25
26 42 KoreaMed. Randomized controlled trials investigating any type of moxibustion treatment
27
28 43 will be included. The primary outcome will be pain intensity and functional status/disability
29
30 44 due to lower back pain. The secondary outcome will be a global measurement of recovery or
31
32 45 improvement, work-related outcomes, radiographic improvement of structure, quality of life,
33
34 46 and adverse events (presence or absence). The Cochrane risk of bias tool will be used to
35
36 47 evaluate methodological quality. Risk ratio or mean differences with a 95% confidence
37
38 48 interval will be used to show the effect of moxibustion therapy when it is possible to conduct
39
40 49 a meta-analysis.

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42 50 **Ethics and Dissemination:** This review will be published in a peer-reviewed journal and will
43
44 51 be presented at an international academic conference for dissemination. Our results will
45
46 52 provide current evidence of the effectiveness and safety of moxibustion treatment in
47
48 53 nonspecific lower back pain patients, and thus will be beneficial to patients, practitioners, and
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50 54 policy makers.

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52 55 **Trial registration number:** CRD42016047468 in PROSPERO 2016
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4 56 **Strengths and limitations of the present study protocol**

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6 57 • Our review provides a systematic, objective, and comprehensive evaluation of the
7
8 58 effectiveness and safety of moxibustion treatment in patients with lower back pain
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10 59 that is nonspecific.
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13 60 • Our review and meta-analysis provide new and useful information for practitioners,
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15 61 policymakers, and patients.
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18 62 • Various treatments with moxibustion and clinical outcomes reviewed in our study will
19
20 63 help to design clinical trial studies of moxibustion treatment for nonspecific lower
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22 64 back pain.
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25 65 • Chinese and Korean databases will be searched to avoid a language bias.
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28 66 • The major limitation of our study protocol is that some of the reviewed trials may
29
30 67 have small sample sizes; this limitation affects our objective and comprehensive
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32 68 assessment of the risks and benefits of moxibustion treatment for nonspecific lower
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34 69 back pain.
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70 INTRODUCTION

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72 More than 70% of people suffer from lower back pain in developed countries[1].
73 Approximately 90% of back pain is nonspecific[2], indicating that most people the
74 pathophysiological origin of the back pain cannot be specified[1]. Moreover, specifying and
75 treating the factor that contributes to lower back pain is difficult because several co-related
76 factors are involved, including psychological, work-related, and other individual factors[3].
77 Back pain is spontaneously relieved, but 5 ~ 20% of acute back pain patients suffer from
78 chronic or persistent lower back pain[4–7]. The widely accepted definition of chronic lower
79 back pain is a pain that persists for more than three months[8]. Even though conventional
80 treatments such as medication or surgery have shown some efficacy against lower back
81 pain[9,10], many lower back pain patients are dissatisfied with conventional treatment[11].

82 The proportion of patients using complementary and alternative medicine to treat lower
83 back is increasing[12]. Acupuncture plays an important role in Traditional East Asian
84 Medicine (TEAM) treatment of pain[13]. Several systematic reviews on the effectiveness and
85 safety of acupuncture treatment in lower back pain patients have been published[14–17].
86 Moxibustion is an important treatment modality in TEAM treatment that stimulates acupoints
87 with the heat energy of a burning herbal preparation[13,18]. Absorption of the therapeutically
88 active components of the herbal preparation also contributes to the effect of moxibustion[18].
89 In TEAM theory, moxibustion treatment promotes qi stimulation and resolves qi stagnation at
90 an acupoint[18]. Two types of moxibustion, direct moxibustion and indirect moxibustion, are
91 widely used in TEAM treatment. Systematic reviews have been published about the
92 effectiveness of moxibustion in several diseases, including insomnia, hypertension, irritable
93 bowel syndrome, and constipation[19–22]. However, systematic review that focuses
94 especially on the effectiveness of moxibustion treatment in nonspecific lower back pain has
95 not been published yet.

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4 96 A systematic review summarizes the evidence of relevant current clinical trial studies; this
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6 97 effort provides supportive information for the design of future clinical trial studies. A
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8 98 systematic review of studies on the effectiveness of Traditional Chinese Medicine (TCM)
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10 99 treatment of back pain was published in 2015[1]. This review of TCM treatment for lower
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12 100 back pain deals with studies involving whole TCM interventions such as acupuncture,
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14 101 acupressure, moxibustion, cupping, Gua Sha, qigong, herbal medicine, and tuina treatments.
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16 102 A focus on moxibustion treatment was beyond the scope of that review, as, no article on
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18 103 moxibustion treatment for back pain was included finally. Thus, the range of interventions
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20 104 that are explored in that previous review is too broad to clarify the critical factors related to
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22 105 moxibustion treatment of lower back pain that are of interest to practitioners and researchers;
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24 106 such factors include the treatment duration, position, intensity, frequency, species of moxa,
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26 107 various outcome parameters, and side effects of moxibustion treatment. A systematic review
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28 108 of studies on the effectiveness of heat sensitive moxibustion treatment for a lumbar disc
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30 109 herniation has also been published[23]. However, as the prevalence of lower back pain that is
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32 110 secondary to a lumbar disc herniation (LDH) is low, it is not our target condition. Only 3 to 4
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34 111 percent of patients with lower back pain who came to a primary clinic suffered from spinal
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36 112 stenosis or a lumbar disc herniation[24]. L5 and S1 spinal nerve root damage due to disc
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38 113 protrusion or degenerative changes in the vertebrae are common causes of lower back pain in
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40 114 patients with a lumbar disc herniation[25]. Hence, nonspecific lower back pain and LDH
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42 115 have different pathophysiologies.

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44 116 Our preliminary search on moxibustion treatment for lower back pain found several clinical
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46 117 studies with various experimental designs; for example, moxibustion versus usual care or
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48 118 conventional treatment, moxibustion versus another TCM intervention such as (electro)
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50 119 acupuncture, and moxibustion adjuvant therapy with acupuncture, among others. Thus, we
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52 120 believe that our study will overcome the limitations of previous systematic reviews of studies
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4 121 involving lower back pain and TCM [1,23].
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6 122 To our knowledge, a systematic review that focuses on the effectiveness of various types of
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8 123 moxibustion treatment for nonspecific lower back pain and includes Chinese and Korean
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10 124 studies has not been published. Thus, we propose to conduct a systematic review that focuses
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12 125 on the effectiveness and safety of moxibustion treatment in patients with nonspecific lower
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14 126 back pain. We will summarize the current evidence and provide useful information to
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16 127 practitioners, patients, and policymakers. A summary of the current evidence from
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18 128 moxibustion clinical trial studies of lower back pain will benefit the development of future
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20 129 moxibustion clinical trial protocols. In the present article, we describe our methods and plan
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22 130 for a systematic review.
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29 132 **Objectives**

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32 133 The objective of the present review is to systematically evaluate the effectiveness and safety
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34 134 of moxibustion treatment compared to placebo control, conventional treatment, or no
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36 135 treatment in nonspecific lower back pain patients evaluated by pain intensity and functional
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38 136 status/disability.
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43 138 **METHODS**

44 139 **Study registration**

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47 140 The systematic review protocol registration number in the International Prospective Register
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49 141 of Systematic Reviews (PROSPERO) is CRD42016047468. This systematic review protocol
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51 142 complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
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53 143 Protocols (PRISMA-P) statement guidelines[26,27]. In addition, our review will be
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55 144 conducted in compliance with the Preferred Reporting Items for Systematic Reviews and
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4 145 Meta-Analyses (PRISMA) statement guidelines[28].
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12 147 **Criteria for study inclusion**

13 148 Type of studies

14 149 We will include only randomized controlled trials (RCT) in this review. Several Chinese trials
15 150 do not provide detailed description of the randomization method used. We will include such
16 151 studies if the authors have mentioned about the randomization method used (随机). However,
17 152 we will grade these studies as high in the “risk of bias assessment” if detailed description on
18 153 the randomization process is not provided. Furthermore, if an incorrect randomization
19 154 method such as coin toss was used, the study will not be included.
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30 156 Type of participants

31 157 Patients diagnosed with only nonspecific lower back pain will be included in the review.

32 158 Trials studies of lower back pain due to other pathologies such as lumbar disc herniation,
33 159 fibromyalgia, tumor, compression fracture, infection, trauma, cauda equine syndrome,
34 160 vertebral canal stenosis, scoliosis, or ankylosing spondylitis will be excluded. There will be
35 161 no restriction of sex, age, ethnicity, disease duration, or disease severity.
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46 163 Type of interventions

47 164 Moxibustion therapy will be compared to a placebo control, conventional treatment, no
48 165 treatment, and an unproven control treatment. Moxibustion adjunctive therapy in combination
49 166 with conventional treatment will be compared to conventional treatment alone. Any type of
50 167 moxibustion will be included, regardless of the treatment frequency, duration, material, type,
51 168 and method. Studies involving direct moxibustion, indirect moxibustion, warm needling,
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4 169 moxa-burner moxibustion, heat sensitive moxibustion, natural moxibustion, herbal patching,
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6 170 and crude drug moxibustion will also be included. Research that compared different
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8 171 moxibustion materials, doses, or durations of moxibustion treatment will not be included.
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10 172 Studies that evaluated the effect of moxibustion with at least 1 day of follow-up will be
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12 173 included.

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19 176 *Primary outcomes.*

21 177 Pain intensity and functional status/disability will be a primary outcome.

23 178 Chief complaints of nonspecific low back pain are pain and functional disability. Moreover,
24 179 there are no objective biomarkers and parameters to evaluate lower back pain. Therefore, we
25 180 selected pain intensity and functional status/disability as primary outcomes. These primary
26 181 outcomes were also widely used in several of the previous systematic reviews on various
27 182 interventions for lower back pain[1,29–33]. Other important outcomes used in these reviews
28 183 were considered secondary outcomes of our review. Pain intensity will be evaluated using the
29 184 visual analogue scale (VAS)[34] or the numerical rating scale (NRS)[35]. As VAS is
30 185 continuous data and NRS is dichotomous data, VAS and NRS will not be mixed in the meta-
31 186 analysis. Functional status/disability will be evaluated using validated measurement tools
32 187 such as the Roland Morris Disability Questionnaire (RMDQ) or the Oswestry Disability
33 188 Scale[36,37].

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37 190 *Secondary outcome.*

39 191 The secondary outcomes will include the following: 1) global measurements of recovery or
40 192 improvement, such as subjective symptom improvement, the proportion of responders,
41 193 overall improvement, and perceived recovery; 2) work-related outcomes, such as productivity,

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4 194 return to work status, and the number of absent days for work; 3) radiographic improvement
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6 195 of structure; 4) quality of life measurements using validated tools such as the Short Form
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8 196 Survey Instrument (SF-36) [38] and Euroqol-5D (EQ-5D) [39]; and 5) complications and
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10 197 adverse events
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15 199 **Search Methods**

17 200 Electronic search

19 201 We will conduct an electronic search of several databases from their inception to December
20 202 2016. Four English databases will be searched, namely, EMBASE (OVID), MEDLINE
21 203 (PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Allied
22 204 and Complementary Medicine Database (AMED); three Chinese database will be searched,
23 205 namely, the Wanfang Database, the Chongqing VIP Chinese Science and Technology
24 206 Periodical Database (VIP), and China National Knowledge Infrastructure Database (CNKI);
25 207 and six Korean databases will be searched, namely, the Korean Medical Database
26 208 (KMBASE), the Korean Studies Information Service System (KISS), National Discovery for
27 209 Science Leaders (NDSL), the Oriental Medicine Advanced Searching Integrated System
28 210 (OASIS), Korea Institute of Science and Technology (KISTI), and KoreaMed. The search
29 211 term will be composed of two parts, moxibustion (e.g., moxibustion or moxabustion or moxa
30 212 or artemisia or mugwort) and back pain (e.g., lower back pain, sciatica, radiculopathy,
31 213 lumbago, backache, back pain, or lumbo-sacral). The online Supplementary Appendix 1
32 214 present our detailed search strategy that will be specific to MEDLINE (PubMed).
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52 216 Searching other resources

53 217 PROSPERO, the International Clinical Trials Registry Platform (ICTRP), and

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55 218 ClinicalTrials.gov will also be searched to identify systematic reviews or ongoing/completed
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4 219 clinical trials. We will conduct a hand search of relevant journals and their conference
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6 220 proceeding. Thesis and bibliographic references of included trials will also be reviewed.
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10 222 **Analysis**

11 223 Study selection

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13 224 Two review authors (J Leem and Y Cho) will independently screen titles and abstracts in
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15 225 retrieved article lists from independent electronic and hand searches to exclude any obviously
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17 226 irrelevant articles. The full text of the remaining articles will be downloaded to assess their
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19 227 eligibility for inclusion in our review according to predefined criteria. Disagreement between
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21 228 these two authors will be resolved by discussion. If these authors do not reach an agreement,
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23 229 a third review author (D Nam) will make the final decision.
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30 231 Data extraction and management

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32 232 Two review authors (J Leem and Y Cho) will read all included articles and extract data
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34 233 according to a predefined data sheet that includes the publication year, author, title, journal,
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36 234 country, hospital setting, study design, allocation concealment, randomization method,
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38 235 blinding, participants number, dropout number, intervention of treatment and control groups,
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40 236 treatment frequency and number, diagnostic criteria, disease duration, disease severity,
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42 237 outcome and results, and adverse event. Disagreement between these two authors will be
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44 238 resolved by discussion. If these authors do not reach an agreement, a third review author (D
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46 239 Nam) will make the final decision. We will request via e-mail that the corresponding author
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48 240 of the original study send data when the results are ambiguous.
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54 242 Assessment of reporting quality and risk of bias

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56 243 Two review authors (J Leem and Y Cho) will independently assess the risk of bias according
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4 244 to the Cochrane risk of bias tool[40] outlined in the Cochrane Handbook for Systematic
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6 245 Reviews for Intervention[41]. Risk of bias assessment categories will include the following:
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8 246 (1) allocation concealment; (2) random sequence generation; (3) blinding of outcome
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10 247 assessors; (4) blinding of participants; (5) incomplete outcome data; (6) selective outcome
11
12 248 reporting; and (7) other biases. The level of the risk of bias will be evaluated as either a low,
13
14 249 high, or unclear risk of bias. Disagreement between these two authors will be resolved by
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16 250 discussion. If these authors do not reach an agreement, a third review author (D Nam) will
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18 251 make the final decision.
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24 253 Unit of analysis

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26 254 If studies measure the same outcome repeatedly, we will perform an analysis according to a
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28 255 timeline definition. Immediate follow-up will mean up to one week after the last intervention.
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30 256 Short-term follow-up will mean from one week to three months. Intermediate-term follow-up
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32 257 will mean from three months to 1 year after the last treatment. Long-term follow-up will
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34 258 mean more than 1 year after the last treatment. If two or more moxibustion treatment arm
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36 259 exist, the number of control group patients will be divided by the number of moxibustion
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38 260 treatment groups and will be synthesized in a meta-analysis
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44 262 Measures of a treatment effect

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46 263 For dichotomous data, a risk ratio (RR) and the 95% confidence (CI) interval will be used to
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48 264 estimate a treatment effect. For continuous data, the mean difference (MD) and the 95% CI
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50 265 will be used to estimate a treatment effect when the same outcome scale or method is used.
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52 266 Standardized mean difference (SMD) and the 95% CI will be used to estimate a treatment
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54 267 effect when a different outcome scale or method is used.
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4 269 Managing missing data

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6 270 We will contact the corresponding author of an article via e-mail to obtain any missing data.

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8 271 If there is no response to an e-mail, we will exclude the data from our analysis, and describe

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10 272 the reason and impact of this exclusion in the Discussion section.

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15 274 Assessment of a reporting bias

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17 275 Publication bias will be assessed visually using funnel plot asymmetry if more than 10

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19 276 articles are included[41]. An Egger's regression test will be used to quantitatively evaluate

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21 277 funnel plot asymmetry[42].

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26 279 Assessment of heterogeneity

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28 280 The heterogeneity of included studies will be quantitatively evaluated using an I^2 statistic that

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30 281 is derived from a chi-square test. The I^2 statistic will be interpreted according to the following

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32 282 criteria: 1) 75-100% will indicate considerable heterogeneity; 2) 50-90% will indicate

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34 283 substantial heterogeneity; 3) 30-60% will indicate moderate heterogeneity; 4) 0-40% will

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36 284 indicate little to no heterogeneity. In this manner, an I^2 statistic of more than 50% will

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38 285 indicate the presence of substantial heterogeneity for the included studies[43]. If the I^2

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40 286 statistic is more than 75%, a meta-analysis will not be conducted[44]. Instead, we will

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42 287 qualitatively describe the effectiveness and safety of moxibustion treatment. If the I^2 statistic

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44 288 belongs to both heterogeneity categories, we will use both adjectives. For example, if I^2

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46 289 statistic is 55%, we will express the heterogeneity as "moderate to substantial heterogeneity."

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53 291 **Data synthesis and grading of quality of evidence**

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55 292 The Review manager (REVMAN) software for Windows will be used to perform a meta-

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57 293 analysis and to calculate the risk ratio or (standardized) mean difference (Version 5.3;

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4 294 Copenhagen; The Nordic Cochrane Center, The Cochrane Collaboration, 2014). We will
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6 295 adopt a random effect model when the I^2 statistic is more than 50%, otherwise we will adopt
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8 296 a fixed effect model in a meta-analysis. If we are unable to conduct meta-analysis due to lack
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10 297 of clinical studies or heterogeneity, we will present the effect size and 95% confidence
11
12 298 interval of every outcome in each clinical trial and describe the meaning of important results
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14 299 in the discussion section qualitatively. To summarize the findings of the meta-analysis and
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16 300 describe the strength of evidence, we will use the Grades of Recommendation, Assessment,
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18 301 Development and Evaluation (GRADE) approach[41].
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24 303 **Subgroup analysis**

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26 304 To identify heterogeneity between the included studies, a subgroup analysis will be
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28 305 conducted if there is sufficient number of articles in each subgroup. The criteria of a
29
30 306 subgroup analysis will be as follows: 1) disease duration, such as chronic (more than 3
31
32 307 months) or acute lower back pain (we will conduct a subgroup analysis according to disease
33
34 308 duration even though there are not sufficient number of included studies); 2) type of control
35
36 309 group, such as placebo moxibustion, conventional treatment, other TCM treatment, and no
37
38 310 treatment; 3) type of moxibustion, such as direct moxibustion, indirect moxibustion, warm
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40 311 needling moxibustion, moxa burner moxibustion, heat sensitive moxibustion, and crude drug
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42 312 moxibustion; 4) species of herb used in the moxibustion treatment; and 5) treatment number,
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44 313 frequency, and duration.
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50 315 **Sensitivity analysis**

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52 316 If there are a sufficient number of included articles, a sensitivity analysis will be carried out
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54 317 after removing low quality articles to identify the robustness of a result. The methodological
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56 318 quality will be assessed according to the “risk of bias” tool[40]. After excluding low quality
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4 319 articles that have more than three “risk of bias categories” graded as “high risk of bias,” we
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6 320 will conduct a second meta-analysis. The results and effect size of the two meta-analyses will
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8 321 be compared and discussed.
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10 322

11 323 **DISCUSSION**

12 324 The purpose of this proposed systematic review and meta-analysis will be to evaluate the
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15 325 effectiveness and safety of moxibustion treatment of nonspecific lower back pain. When
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17 326 compared to acupuncture research, the quantity and quality of moxibustion therapy research
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19 327 is relatively low. The STandards for Reporting Interventions in Clinical Trials of Moxibustion
20
21 328 (STRICTOM) was published in Chinese in 2013[45], but has not been widely adopted and
22
23 329 translated into English. A recent systematic review was published on TCM treatment of lower
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25 330 back pain[1]. This review included a variety of interventions that are practiced in TCM, such
26
27 331 as acupuncture, moxibustion, herbal medicine, cupping, and manual therapy, among others.
28
29 332 However, the various interventions that were included in that review have too broad of a
30
31 333 range to appropriately evaluate the issues that are specific to moxibustion treatment of lower
32
33 334 back pain. Moreover, it did not include any trial studies of moxibustion treatment. A
34
35 335 systematic review has also been published regarding the effectiveness of heat sensitive
36
37 336 moxibustion for lumbar disc herniation[23]. However, this review is not concerned with
38
39 337 nonspecific back pain, but rather, lower back pain that is secondary to lumbar disc herniation.
40
41 338 Therefore, the protocol described here is for the first systematic review and meta-analysis on
42
43 339 the effectiveness and safety of any type of moxibustion treatment in nonspecific lower back
44
45 340 pain patients. We anticipate that our review and meta-analysis will provide useful information
46
47 341 to practitioners, policymakers, and patients.
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12 460 **AUTHORS' CONTRIBUTIONS**

13
14 461 Dongwoo Nam conceived of the study. The protocol was drafted by Jungtae Leem and Yeeun
15 462 Cho. The search strategy was developed by Seunghoon Lee and Sanghoon Lee. The inclusion
16 463 criteria were developed by Yeoncheol Parka and Byungkwan Seo. The authors Jungwon
17 464 Kang and Eun-jung Kim revised the manuscript. The authors Yoonjae Lee, In-Hyuk Ha, and
18 465 Hyun-jong Lee developed the analysis plan. Jungtae Leem submitted the manuscript for
19 466 publication. All authors have read and approved the final manuscript.

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26 471

27 472 **COMPETING INTERESTS**

28
29 473 The authors declare no competing interests.

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31 474

32 475 **PROVENANCE AND PEER REVIEW**

33
34 476 Not commissioned; externally peer reviewed.

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Appendix 1 :

[MEDLINE(Pubmed) Search Strategy]

- #1 Low Back Pain/
#2 Sciatica/
#3 Radiculopathy/
#4 (lumbar OR lumbosacral OR lumbo-sacral OR back) adj5 (pain* OR ache* OR aching) [TIAB]
#5 backache*[TIAB] OR lumbago[TIAB] OR sciatica[TIAB]
#6 radiculopathy[TIAB] OR radiculitis[TIAB] OR radicular pain*[TIAB]
#7 (nerve root* adj5 (pain* OR avulsion OR compress* OR disorder* OR pinch* OR inflam* OR imping* OR irritat* OR entrap* OR trap*)) [TIAB]
#8 {or #6-#7}
#9 back*[TIAB] OR lumbosacral[TIAB] OR lumbo-sacral[TIAB] OR lumbar[TIAB]
#10 #8 and #9
#11 {or #1-#5, #10}
#12 Moxibustion/
#13 Artemisia/
#14 (moxibustion or moxabustion or moxa or artemisia or mugwort\$.tw.
#15 {or #12-#14}
#16 #11 and #15
#17 randomized controlled trial [PT]
#18 controlled clinical trial [PT]
#19 randomized [TIAB]
#20 placebo [TIAB]
#21 clinical trials as topic [mesh: noexp]

1
2
3
4 #22 randomly [TIAB]
5
6

7 #23 trial [TI]
8

9 #24 {or #17-#23}
10

11 #25 animals [mh] NOT humans [mh]
12

13 #26 #24 NOT #25
14

15 #27 #16 and #26
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21 [CENTRAL (cochrane) Search Strategy]
22

23 #1 MeSH descriptor: [Low Back Pain] explode all trees
24

25 #2 MeSH descriptor: [Sciatica] explode all trees
26

27 #3 MeSH descriptor: [Radiculopathy] explode all trees
28

29 #4 (lumbar or lumbosacral or lumbo-sacral or back) near/5 (pain* or ache* or
30
31
32 aching):ti,ab,kw (Word variations have been searched)
33

34 #5 backache* or lumbago or sciatica:ti,ab,kw (Word variations have been searched)
35

36 #6 radiculopathy or radiculitis or radicular pain*:ti,ab,kw (Word variations have been
37
38
39 searched)
40

41 #7 (nerve root* near/5 (pain* or avulsion or compress* or disorder* or pinch* or
42
43
44 inflam* or imping* or irritat* or entrap* or trap*)):ti,ab,kw (Word variations have been
45
46
47 searched)
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49 #8 {or #6-#7}
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51 #9 back* or lumbosacral or lumbo-sacral or lumbar:ti,ab,kw (Word variations have been
52
53
54 searched)
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56 #10 #8 and #9
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58 #11 {or #1-#5, #10}
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60 #12 MeSH descriptor: [Moxibustion] explode all trees

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4 #13 MeSH descriptor: [Artemisia] explode all trees
5
6 #14 moxibustion or moxabustion or moxa or artemisia or mugwort\$:ti,ab,kw (Word
7
8 variations have been searched)
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11 #15 {or #12-#14}
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13 #16 #11 and #15
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15 #17 (Select only trials)
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23 [EMBASE Search Strategy]
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- 28 #1 'Low Back Pain'/exp
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30 #2 'Sciatica'/exp
31
32 #3 'Radiculopathy'/exp
33
34 #4 ((lumbar OR lumbosacral OR 'lumbo sacral' OR back) NEAR/5 (pain* OR ache* OR
35 aching)):ab,ti
36
37 #5 (backache* or lumbago or sciatica):ab,ti
38
39 #6 (radiculopathy or radiculitis or radicular pain*):ab,ti
40
41 #7 (nerve root* NEAR/5 (pain* or avulsion or compress* or disorder* or pinch* or
42 inflam* or imping* or irritat* or entrap* or trap*)):ab,ti
43
44 #8 {or #6-#7}
45
46 #9 (back* or lumbosacral or lumbo-sacral or lumbar):ab,ti
47
48 #10 #8 and #9
49
50 #11 {or #1-#5, #10}
51
52 #12 Moxibustion/exp
53
54 #13 Artemisia/exp
55
56 #14 (moxibustion or moxabustion or moxa or artemisia or mugwort\$):ab,ti
57
58 #15 {or #12-#14}
59
60 #16 #11 and #15

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5 #17 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled
6 trial':de OR 'single-blind procedure':de OR (random* OR factorial* OR crossover* OR cross
7 NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR
8 assign* OR allocat* OR volunteer*):de,ab,ti
9

10 #18 #16 and #17
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14 [Chinese database search strategy : CNKI, VIP, Wanfang]
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17
18 #1 腰痛 and 灸
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21 #2 坐骨神经痛 and 灸
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24 #3 神经根型颈椎病 and 灸
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27 #4 腰椎 and 灸
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29
30 #5 腰骶部 and 灸
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32
33 #6 背痛 and 灸
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36 #7 神经根炎 and 灸
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39 #8 神经根性疼痛 and 灸
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41
42 #9 神经根 and 灸
43

44
45 #10 腰痛 and 艾
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47
48 #11 坐骨神经痛 and 艾
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51 #12 神经根型颈椎病 and 艾
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54 #13 腰椎 and 艾
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57 #14 腰骶部 and 艾
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60 #15 背痛 and 艾
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#16 神经根炎 and 艾
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#17 神经根性疼痛 and 艾
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5 #18 神经根 and 艾
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8 #19 腰痛 and 蒿
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10 #20 坐骨神经痛 and 蒿
11

12 #21 神经根型颈椎病 and 蒿
13

14
15 #22 腰椎 and 蒿
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17
18 #23 腰骶部 and 蒿
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20 #24 背痛 and 蒿
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22
23 #25 神经根炎 and 蒿
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26 #26 神经根性疼痛 and 蒿
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28 #27 神经根 and 蒿
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30 #28 or/#1-#27
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PRISMA- P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input type="checkbox"/>		1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			Not update for previous review
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input type="checkbox"/>		55
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input type="checkbox"/>		5-30
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input type="checkbox"/>		475-479
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments			Not amendment for previous review
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input type="checkbox"/>		468-470
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>		468-470
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol			No roles exist
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input type="checkbox"/>		96-130

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input type="checkbox"/>		133-136
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input type="checkbox"/>		148-197
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input type="checkbox"/>		199-214
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input type="checkbox"/>		199-214
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input type="checkbox"/>		222-240
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input type="checkbox"/>		223-229
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input type="checkbox"/>		231-240
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input type="checkbox"/>		231-240
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input type="checkbox"/>		176-197
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input type="checkbox"/>		242-251
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>		291-301
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input type="checkbox"/>		279-301

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input type="checkbox"/>		303-321
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>		291-301
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input type="checkbox"/>		274-277
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>		291-301

BMJ Open

Effectiveness and safety of moxibustion treatment for nonspecific lower back pain: protocol for a systematic review

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014936.R2
Article Type:	Protocol
Date Submitted by the Author:	15-Apr-2017
Complete List of Authors:	<p>Leem, Jungtae; Kyung Hee University, Department of Clinical Korean Medicine</p> <p>Lee, Seunghoon; Kyung Hee University Korean Medicine Hospital, Dept. of Acupuncture & Moxibustion Medicine</p> <p>Park, Yeon Cheol; Kyung Hee University Hospital at Gangdong, Acupuncture & Moxibustion</p> <p>Seo, Byung-Kwan; Kyung Hee University Hospital at Gangdong, Acupuncture & Moxibustion</p> <p>Cho, Yeeun; Kyung Hee University Korean Medicine Hospital, Dept. of Acupuncture & Moxibustion Medicine</p> <p>Kang, Jung Won; Kyung Hee University, Acupuncture & Moxibustion Medicine</p> <p>Lee, Yoon Jae; Jaseng Medical Foundation, Jaseng Spine and Joint Research Institute</p> <p>Ha, In-Hyuk; Jaseng Medical Foundation, Jaseng Spine and Joint Research Institute</p> <p>Lee, Hyun- jong ; Daegu Oriental hospital of Daegu Haany University, Department of Acupuncture & Moxibustion medicine</p> <p>Kim, Eun-jung; Dongguk University, Dept. of Acupuncture & Moxibustion, College of Oriental Medicin</p> <p>Lee, Sanghoon; Kyung Hee University, Dept. of Acupuncture & Moxibustion, College of Korean Medicine; Kyung Hee University, Dept. of Clinical Korean Medicine, Graduate School</p> <p>Nam, Dongwoo; Kyung Hee University, Department of Acupuncture & Moxibustion</p>
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, moxibustion, systematic review, meta analysis, traditional medicine

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Manuscripts

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1 **Effectiveness and safety of moxibustion treatment**
2 **for nonspecific lower back pain: protocol for a**
3 **systematic review**

4
5 Jungtae Leem^{1,2}, Seunghoon Lee³, Yeoncheol Park⁴, Byungkwan Seo^{4,5}, Yeeun Cho³,
6 Jungwon Kang^{3,5}, Yoonjae Lee⁶, In-Hyuk Ha⁶, Hyun-jong Lee⁷, Eun-jung Kim⁸, Sanghoon
7 Lee^{1,3,5}, and Dongwoo Nam^{3,5*}

8
9 ¹Department of Clinical Korean Medicine, Graduate School, Kyung Hee University, 26
10 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea

11 ²Korean Medicine Clinical Trial Center, Kyung Hee University Korean Medicine Hospital,
12 23 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea

13 ³Department of Acupuncture & Moxibustion Medicine, Kyung Hee University Korean
14 Medicine Hospital, 23 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea

15 ⁴Department of Acupuncture & Moxibustion, Kyung Hee University Hospital at Gangdong,
16 892 Dongnam-ro, Gangdong-gu, Seoul, 05278, South Korea.

17 ⁵Department of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee
18 University, 26 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea.

19 ⁶Jaseng Spine and Joint Research Institute, Jaseng Medical Foundation, 858 Eonju-ro,
20 Gangnam-gu, Seoul, 06017, South Korea.

21 ⁷Department of Acupuncture & Moxibustion, College of Korean Medicine, Daegu Haany
22 University, Haanydaero 1, Gyeongsan-si, Gyeongsangbuk-do, 38610, South Korea.

23 ⁸Department of Acupuncture & Moxibustion, College of Oriental Medicine, Dongguk

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24 University, 268 Buljeong-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, 13601, South Korea

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26 ***Correspondence to**

27 Dongwoo Nam, KMD, PhD

28 Department. of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee

29 University, 26 Kyungheedaero, Dongdaemun-gu, Seoul, 02447, South Korea

30 Telephone: + 82-2-958-9207, Fax: + 82-2-958-8169, E-mail: hanisanam@daum.net

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4 31 **ABSTRACT**

5
6 32 **Introduction:** Many patients experience acute lower back pain that becomes chronic pain.
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9 33 The proportion of patients using complementary and alternative medicine to treat lower back
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11 34 is increasing. Even though several moxibustion clinical trials for lower back pain have been
12
13 35 conducted, the effectiveness and safety of moxibustion intervention is controversial. The
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15 36 Purpose of this study protocol for a systematic review is to evaluate the effectiveness and
16
17 37 safety of moxibustion treatment for nonspecific lower back pain patients.

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19 38 **Methods and Analysis:** We will conduct an electronic search of several databases from their
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21 39 inception to May 2017, including EMBASE, PubMed, Cochrane Central Register of
22
23 40 Controlled Trial, Allied and Complementary Medicine Database, Wanfang Database,
24
25 41 Chongqing VIP Chinese Science and Technology Periodical Database, China National
26
27 42 Knowledge Infrastructure Database, Korean Medical Database, Korean Studies Information
28
29 43 Service System, National Discovery for Science Leaders, Oriental Medicine Advanced
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31 44 Searching Integrated System, the Korea Institute of Science and Technology, and KoreaMed.
32
33 45 Randomized controlled trials investigating any type of moxibustion treatment will be
34
35 46 included. The primary outcome will be pain intensity and functional status/disability due to
36
37 47 lower back pain. The secondary outcome will be a global measurement of recovery or
38
39 48 improvement, work-related outcomes, radiographic improvement of structure, quality of life,
40
41 49 and adverse events (presence or absence). Risk ratio or mean differences with a 95%
42
43 50 confidence interval will be used to show the effect of moxibustion therapy when it is possible
44
45 51 to conduct a meta-analysis.

46
47 52 **Ethics and Dissemination:** This review will be published in a peer-reviewed journal and will
48
49 53 be presented at an international academic conference for dissemination. Our results will
50
51 54 provide current evidence of the effectiveness and safety of moxibustion treatment in
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53 55 nonspecific lower back pain patients, and thus will be beneficial to patients, practitioners, and
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56 policy makers.

57 **Trial registration number:** CRD42016047468 in PROSPERO 2016

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4 58 **Strengths and limitations of the present study protocol**

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6 59 • Our review provides a systematic, objective, and comprehensive evaluation of the
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8 60 effectiveness and safety of moxibustion treatment in patients with lower back pain
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10 61 that is nonspecific.
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13 62 • Our review and meta-analysis provide new and useful information for practitioners,
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15 63 policymakers, and patients.
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18 64 • Various treatments with moxibustion and clinical outcomes reviewed in our study will
19
20 65 help to design clinical trial studies of moxibustion treatment for nonspecific lower
21
22 66 back pain.
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25 67 • Chinese and Korean databases will be searched to avoid a language bias.
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28 68 • The major limitation of our study protocol is that some of the reviewed trials may
29
30 69 have small sample sizes; this limitation affects our objective and comprehensive
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32 70 assessment of the risks and benefits of moxibustion treatment for nonspecific lower
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34 71 back pain.
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72 INTRODUCTION

73
74 More than 70% of people suffer from lower back pain in developed countries[1].
75 Approximately 90% of back pain is nonspecific[2], indicating that most people the
76 pathophysiological origin of the back pain cannot be specified[1]. Moreover, specifying and
77 treating the factor that contributes to lower back pain is difficult because several co-related
78 factors are involved, including psychological, work-related, and other individual factors[3].
79 Back pain is spontaneously relieved, but 5 ~ 20% of acute back pain patients suffer from
80 chronic or persistent lower back pain[4–7]. The widely accepted definition of chronic lower
81 back pain is a pain that persists for more than three months[8]. Even though conventional
82 treatments such as medication or surgery have shown some efficacy against lower back
83 pain[9,10], many lower back pain patients are dissatisfied with conventional treatment[11].

84 The proportion of patients using complementary and alternative medicine to treat lower
85 back is increasing[12]. Acupuncture plays an important role in Traditional East Asian
86 Medicine (TEAM) treatment of pain[13]. Several systematic reviews on the effectiveness and
87 safety of acupuncture treatment in lower back pain patients have been published[14–17].
88 Moxibustion is an important treatment modality in TEAM treatment that stimulates acupoints
89 with the heat energy of a burning herbal preparation[13,18]. Absorption of the therapeutically
90 active components of the herbal preparation also contributes to the effect of moxibustion[18].
91 In TEAM theory, moxibustion treatment promotes qi stimulation and resolves qi stagnation at
92 an acupoint[18]. Two types of moxibustion, direct moxibustion and indirect moxibustion, are
93 widely used in TEAM treatment. Systematic reviews have been published about the
94 effectiveness of moxibustion in several diseases, including insomnia, hypertension, irritable
95 bowel syndrome, and constipation[19–22]. However, a systematic review that focuses
96 especially on the effectiveness of moxibustion treatment in nonspecific lower back pain has
97 not been published yet.

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4 98 A systematic review summarizes the evidence of relevant current clinical trial studies; this
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6 99 effort provides supportive information for the design of future clinical trial studies. A
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9 100 systematic review of studies on the effectiveness of Traditional Chinese Medicine (TCM)
10
11 101 treatment of back pain was published in 2015[1]. This review of TCM treatment for lower
12
13 102 back pain deals with studies involving whole TCM interventions such as acupuncture,
14
15 103 acupressure, moxibustion, cupping, Gua Sha, qigong, herbal medicine, and tuina treatments.
16
17 104 However, the focus of that review was only pain intensity and disability measured with
18
19 105 continuous outcome variables such as the visual analogue scale. There were no articles on
20
21 106 moxibustion treatment for lower back pain included in the review; however, other parameters
22
23 107 such as quality of life, work related outcome, side effects, and the proportion of responders
24
25 108 are also important and valuable clinical outcome variables in patients with lower back pain. If
26
27 109 we do not restrict outcome measures to only the intensity of pain and disability measured by
28
29 110 continuous outcome variables, we can identify more moxibustion clinical trials and include
30
31 111 Korean databases since moxibustion therapy is widely used in Korea for the treatment of
32
33 112 lower back pain. The last search by the previous review was conducted in 2014; however,
34
35 113 additional clinical trials have been conducted since. Thus, we could include and analyze more
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37 114 moxibustion clinical trials than did the previous review. And the range of interventions that
38
39 115 are explored in that previous review is too broad to clarify the critical factors related to
40
41 116 moxibustion treatment of lower back pain that are of interest to practitioners and researchers;
42
43 117 such factors include the treatment duration, position, intensity, frequency, species of moxa,
44
45 118 various outcome parameters, and side effects of moxibustion treatment. A systematic review
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47 119 of studies on the effectiveness of heat sensitive moxibustion treatment for a lumbar disc
48
49 120 herniation has also been published[23]. However, as the prevalence of lower back pain that is
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51 121 secondary to a lumbar disc herniation (LDH) is low, it is not our target condition. Only 3 to 4
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53 122 percent of patients with lower back pain who came to a primary clinic suffered from spinal
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4 123 stenosis or a lumbar disc herniation[24]. L5 and S1 spinal nerve root damage due to disc
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6 124 protrusion or degenerative changes in the vertebrae are common causes of lower back pain in
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8 125 patients with a lumbar disc herniation[25]. Hence, nonspecific lower back pain and LDH
9
10 126 have different pathophysiologies.

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13 127 Our preliminary search on moxibustion treatment for lower back pain found several clinical
14
15 128 studies with various experimental designs; for example, moxibustion versus usual care or
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17 129 conventional treatment, moxibustion versus another TCM intervention such as (electro)
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19 130 acupuncture, and moxibustion adjuvant therapy with acupuncture, among others. Thus, we
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21 131 believe that our study will overcome the limitations of previous systematic reviews of studies
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23 132 involving lower back pain and TCM [1,23].

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26 133 To our knowledge, a systematic review that focuses on the effectiveness of various types of
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28 134 moxibustion treatment for nonspecific lower back pain and includes Chinese and Korean
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30 135 studies has not been published. Thus, we propose to conduct a systematic review that focuses
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32 136 on the effectiveness and safety of moxibustion treatment in patients with nonspecific lower
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34 137 back pain. We will summarize the current evidence and provide useful information to
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36 138 practitioners, patients, and policymakers. A summary of the current evidence from
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38 139 moxibustion clinical trial studies of lower back pain will benefit the development of future
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40 140 moxibustion clinical trial protocols. In the present article, we describe our methods and plan
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42 141 for a systematic review.

43 44 45 46 142 47 48 49 143 **Objectives**

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52 144 The objective of the present review is to systematically evaluate the effectiveness and safety
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54 145 of moxibustion treatment compared to placebo control, conventional treatment, or no
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56 146 treatment in nonspecific lower back pain patients evaluated by pain intensity and functional
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149 **METHODS**

150 **Study registration**

151 The systematic review protocol registration number in the International Prospective Register
152 of Systematic Reviews (PROSPERO) is CRD42016047468. This systematic review protocol
153 complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
154 Protocols (PRISMA-P) statement guidelines[26,27]. In addition, our review will be
155 conducted in compliance with the Preferred Reporting Items for Systematic Reviews and
156 Meta-Analyses (PRISMA) statement guidelines[28].

157

158 **Criteria for study inclusion**

159 Type of studies

160 We will include only randomized controlled trials (RCT) in this review. Several Chinese trials
161 do not provide detailed description of the randomization method used. We will include such
162 studies if the authors have mentioned about the randomization method used (随机). However,
163 we will grade these studies as high in the “risk of bias assessment” if detailed description on
164 the randomization process is not provided. Furthermore, if an incorrect randomization
165 method such as coin toss was used, the study will not be included.

166

167 Type of participants

168 Patients diagnosed with only nonspecific lower back pain will be included in the review.
169 Trials studies of lower back pain due to other pathologies such as lumbar disc herniation,
170 fibromyalgia, tumor, compression fracture, infection, trauma, cauda equine syndrome,

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4 171 vertebral canal stenosis, scoliosis, or ankylosing spondylitis will be excluded. There will be
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6 172 no restriction of sex, age, ethnicity, disease duration, or disease severity.
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10 174 Type of interventions
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12 175 Moxibustion therapy will be compared to a placebo control, conventional treatment, no
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14 176 treatment, and an unproven control treatment. Moxibustion adjunctive therapy in combination
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16 177 with conventional treatment will be compared to conventional treatment alone. Any type of
17
18 178 moxibustion will be included, regardless of the treatment frequency, duration, material, type,
19
20 179 and method. Studies involving direct moxibustion, indirect moxibustion, warm needling,
21
22 180 moxa-burner moxibustion, heat sensitive moxibustion, natural moxibustion, herbal patching,
23
24 181 and crude drug moxibustion will also be included. Research that compares different
25
26 182 moxibustion materials, doses, or durations of moxibustion treatment will not be included.
27
28 183 Studies that evaluated the effect of moxibustion with at least 1 day of follow-up will be
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30 184 included.
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36 187 *Primary outcomes.*
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38 188 Pain intensity and functional status/disability will be a primary outcome.
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40 189 Chief complaints of nonspecific low back pain are pain and functional disability. Moreover,
41
42 190 there are no objective biomarkers and parameters to evaluate lower back pain. Therefore, we
43
44 191 selected pain intensity and functional status/disability as primary outcomes. These primary
45
46 192 outcomes were also widely used in several of the previous systematic reviews on various
47
48 193 interventions for lower back pain[1,29–33]. Other important outcomes used in these reviews
49
50 194 were considered secondary outcomes of our review. Pain intensity will be evaluated using the
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52 195 visual analogue scale (VAS)[34] or the numerical rating scale (NRS)[35]. As VAS is
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4 196 continuous data and NRS is dichotomous data, VAS and NRS will not be mixed in the meta-
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6 197 analysis. Functional status/disability will be evaluated using validated measurement tools
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8 198 such as the Roland Morris Disability Questionnaire (RMDQ) or the Oswestry Disability
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10 199 Scale[36,37].
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15 201 *Secondary outcome.*

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17 202 The secondary outcomes will include the following: 1) global measurements of recovery or
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19 203 improvement, such as subjective symptom improvement, the proportion of responders,
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21 204 overall improvement, and perceived recovery; 2) work-related outcomes, such as productivity,
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23 205 return to work status, and the number of absent days for work; 3) radiographic improvement
24
25 206 of structure; 4) quality of life measurements using validated tools such as the Short Form
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27 207 Survey Instrument (SF-36) [38] and Euroqol-5D (EQ-5D) [39]; and 5) complications and
28
29 208 adverse events
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33 210 **Search Methods**

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35 211 Electronic search

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37 212 We will conduct an electronic search of several databases from their inception to May 2017.

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39 213 Four English databases will be searched, namely, EMBASE (OVID), MEDLINE (PubMed),

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41 214 the Cochrane Central Register of Controlled Trials (CENTRAL), and the Allied and

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43 215 Complementary Medicine Database (AMED); three Chinese database will be searched,

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45 216 namely, the Wanfang Database, the Chongqing VIP Chinese Science and Technology

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47 217 Periodical Database (VIP), and China National Knowledge Infrastructure Database (CNKI);

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49 218 and six Korean databases will be searched, namely, the Korean Medical Database

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51 219 (KMBASE), the Korean Studies Information Service System (KISS), National Discovery for

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53 220 Science Leaders (NDSL), the Oriental Medicine Advanced Searching Integrated System
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4 221 (OASIS), Korea Institute of Science and Technology (KISTI), and KoreaMed. The search
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6 222 term will be composed of two parts, moxibustion (e.g., moxibustion or moxabustion or moxa
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8 223 or artemisia or mugwort) and back pain (e.g., lower back pain, sciatica, radiculopathy,
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10 224 lumbago, backache, back pain, or lumbo-sacral). The online Supplementary Appendix 1
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12 225 present our detailed search strategy that will be specific to MEDLINE (PubMed).
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17 227 Searching other resources

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19 228 PROSPERO, the International Clinical Trials Registry Platform (ICTRP), and
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21 229 ClinicalTrials.gov will also be searched to identify systematic reviews or ongoing/completed
22
23 230 clinical trials. We will conduct a hand search of relevant journals and their conference
24
25 231 proceeding. Thesis and bibliographic references of included trials will also be reviewed.
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30 233 **Analysis**

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32 234 Study selection

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34 235 Two review authors (J Leem and Y Cho) will independently screen titles and abstracts in
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36 236 retrieved article lists from independent electronic and hand searches to exclude any obviously
37
38 237 irrelevant articles. The full text of the remaining articles will be downloaded to assess their
39
40 238 eligibility for inclusion in our review according to predefined criteria. Disagreement between
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42 239 these two authors will be resolved by discussion. If these authors do not reach an agreement,
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44 240 a third review author (D Nam) will make the final decision.
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50 242 Data extraction and management

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52 243 Two review authors (J Leem and Y Cho) will read all included articles and extract data
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54 244 according to a predefined data sheet that includes the publication year, author, title, journal,
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56 245 country, hospital setting, study design, allocation concealment, randomization method,
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4 246 blinding, participants number, dropout number, intervention of treatment and control groups,
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6 247 treatment frequency and number, diagnostic criteria, disease duration, disease severity,
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8 248 outcome and results, and adverse event. Disagreement between these two authors will be
9
10 249 resolved by discussion. If these authors do not reach an agreement, a third review author (D
11
12 250 Nam) will make the final decision. We will request via e-mail that the corresponding author
13
14 251 of the original study send data when the results are ambiguous.
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20 253 Assessment of reporting quality and risk of bias

21
22 254 Two review authors (J Leem and Y Cho) will independently assess the risk of bias according
23
24 255 to the Cochrane risk of bias tool[40] outlined in the Cochrane Handbook for Systematic
25
26 256 Reviews for Intervention[41]. Risk of bias assessment categories will include the following:
27
28 257 (1) allocation concealment; (2) random sequence generation; (3) blinding of outcome
29
30 258 assessors; (4) blinding of participants; (5) incomplete outcome data; (6) selective outcome
31
32 259 reporting; and (7) other biases. The level of the risk of bias will be evaluated as either a low,
33
34 260 high, or unclear risk of bias. Disagreement between these two authors will be resolved by
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36 261 discussion. If these authors do not reach an agreement, a third review author (D Nam) will
37
38 262 make the final decision.
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44 264 Unit of analysis

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46 265 If studies measure the same outcome repeatedly, we will perform an analysis according to a
47
48 266 timeline definition. Immediate follow-up will mean up to one week after the last intervention.
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50 267 Short-term follow-up will mean from one week to three months. Intermediate-term follow-up
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52 268 will mean from three months to 1 year after the last treatment. Long-term follow-up will
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54 269 mean more than 1 year after the last treatment. If two or more moxibustion treatment arm
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56 270 exist, the number of control group patients will be divided by the number of moxibustion
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4 271 treatment groups and will be synthesized in a meta-analysis

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8 273 Measures of a treatment effect

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10 274 For dichotomous data, a risk ratio (RR) and the 95% confidence (CI) interval will be used to

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12 275 estimate a treatment effect. For continuous data, the mean difference (MD) and the 95% CI

13
14 276 will be used to estimate a treatment effect when the same outcome scale or method is used.

15
16 277 Standardized mean difference (SMD) and the 95% CI will be used to estimate a treatment

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18 278 effect when a different outcome scale or method is used.

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22 280 Managing missing data

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24 281 We will contact the corresponding author of an article via e-mail to obtain any missing data.

25
26 282 If there is no response to an e-mail, we will exclude the data from our analysis, and describe

27
28 283 the reason and impact of this exclusion in the Discussion section.

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32 285 Assessment of a reporting bias

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34 286 Publication bias will be assessed visually using funnel plot asymmetry if more than 10

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36 287 articles are included[41]. An Egger's regression test will be used to quantitatively evaluate

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38 288 funnel plot asymmetry[42].

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42 290 Assessment of heterogeneity

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44 291 The heterogeneity of included studies will be quantitatively evaluated using an I^2 statistic that

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46 292 is derived from a chi-square test. The I^2 statistic will be interpreted according to the following

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48 293 criteria: 1) 75-100% will indicate considerable heterogeneity; 2) 50-90% will indicate

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50 294 substantial heterogeneity; 3) 30-60% will indicate moderate heterogeneity; 4) 0-40% will

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52 295 indicate little to no heterogeneity. In this manner, an I^2 statistic of more than 50% will

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4 296 indicate the presence of substantial heterogeneity for the included studies[43]. If the I^2
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6 297 statistic is more than 75%, a meta-analysis will not be conducted[44]. Instead, we will
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8 298 qualitatively describe the effectiveness and safety of moxibustion treatment. If the I^2 statistic
9
10 299 belongs to both heterogeneity categories, we will use both adjectives. For example, if I^2
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12 300 statistic is 55%, we will express the heterogeneity as “moderate to substantial heterogeneity.”
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302 **Data synthesis and grading of quality of evidence**

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19 303 The Review manager (REVMAN) software for Windows will be used to perform a meta-
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21 304 analysis and to calculate the risk ratio or (standardized) mean difference (Version 5.3;
22
23 305 Copenhagen; The Nordic Cochrane Center, The Cochrane Collaboration, 2014). We will
24
25 306 adopt a random effect model when the I^2 statistic is more than 50%, otherwise we will adopt
26
27 307 a fixed effect model in a meta-analysis. If we are unable to conduct meta-analysis due to lack
28
29 308 of clinical studies or heterogeneity, we will present the effect size and 95% confidence
30
31 309 interval of every outcome in each clinical trial and describe the meaning of important results
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33 310 in the discussion section qualitatively. To summarize the findings of the meta-analysis and
34
35 311 describe the strength of evidence, we will use the Grades of Recommendation, Assessment,
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37 312 Development and Evaluation (GRADE) approach[41].
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44 **Subgroup analysis**

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46 315 To identify heterogeneity between the included studies, a subgroup analysis will be
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48 316 conducted if there is sufficient number of articles in each subgroup. The criteria of a
49
50 317 subgroup analysis will be as follows: 1) disease duration, such as chronic (more than 3
51
52 318 months) or acute lower back pain (we will conduct a subgroup analysis according to disease
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54 319 duration even though there are not sufficient number of included studies); 2) type of control
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56 320 group, such as placebo moxibustion, conventional treatment, other TCM treatment, and no
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4 321 treatment; 3) type of moxibustion, such as direct moxibustion, indirect moxibustion, warm
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6 322 needling moxibustion, moxa burner moxibustion, heat sensitive moxibustion, and crude drug
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8 323 moxibustion; 4) species of herb used in the moxibustion treatment; and 5) treatment number,
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10 324 frequency, and duration.
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14 325 15 326 **Sensitivity analysis**

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17 327 If there are a sufficient number of included articles, a sensitivity analysis will be carried out
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19 328 after removing low quality articles to identify the robustness of a result. The methodological
20
21 329 quality will be assessed according to the “risk of bias” tool[40]. After excluding low quality
22
23 330 articles that have more than three “risk of bias categories” graded as “high risk of bias,” we
24
25 331 will conduct a second meta-analysis. The results and effect size of the two meta-analyses will
26
27 332 be compared and discussed.
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31 333 32 33 334 **DISCUSSION**

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35 335 The purpose of this proposed systematic review and meta-analysis will be to evaluate the
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37 336 effectiveness and safety of moxibustion treatment of nonspecific lower back pain. When
38
39 337 compared to acupuncture research, the quantity and quality of moxibustion therapy research
40
41 338 is relatively low. The STandards for Reporting Interventions in Clinical Trials of Moxibustion
42
43 339 (STRICTOM) was published in Chinese in 2013[45], but has not been widely adopted and
44
45 340 translated into English. A recent systematic review was published on TCM treatment of lower
46
47 341 back pain[1]. This review included a variety of interventions that are practiced in TCM, such
48
49 342 as acupuncture, moxibustion, herbal medicine, cupping, and manual therapy, among others.
50
51 343 However, the various interventions that were included in that review have too broad of a
52
53 344 range to appropriately evaluate the issues that are specific to moxibustion treatment of lower
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55 345 back pain. Moreover, it did not include any trial studies of moxibustion treatment. A
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4 346 systematic review has also been published regarding the effectiveness of heat sensitive
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6 347 moxibustion for lumbar disc herniation[23]. However, this review is not concerned with
7
8 348 nonspecific back pain, but rather, lower back pain that is secondary to lumbar disc herniation.
9
10 349 Therefore, the protocol described here is for the first systematic review and meta-analysis on
11
12 350 the effectiveness and safety of any type of moxibustion treatment in nonspecific lower back
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14 351 pain patients. We anticipate that our review and meta-analysis will provide useful information
15
16 352 to practitioners, policymakers, and patients.
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471 **AUTHORS’ CONTRIBUTIONS**

472 Dongwoo Nam conceived of the study. The protocol was drafted by Jungtae Leem and Yeeun
473 Cho. The search strategy was developed by Seunghoon Lee and Sanghoon Lee. The inclusion
474 criteria were developed by Yeoncheol Parka and Byungkwan Seo. The authors Jungwon
475 Kang and Eun-jung Kim revised the manuscript. The authors Yoonjae Lee, In-Hyuk Ha, and
476 Hyun-jong Lee developed the analysis plan. Jungtae Leem submitted the manuscript for
477 publication. All authors have read and approved the final manuscript.

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482

483 **COMPETING INTERESTS**

484 The authors declare no competing interests.

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486 **PROVENANCE AND PEER REVIEW**

487 Not commissioned; externally peer reviewed.

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For peer review only

Appendix 1 :

[MEDLINE(Pubmed) Search Strategy]

- #1 Low Back Pain/
#2 Sciatica/
#3 Radiculopathy/
#4 (lumbar OR lumbosacral OR lumbo-sacral OR back) adj5 (pain* OR ache* OR aching) [TIAB]
#5 backache*[TIAB] OR lumbago[TIAB] OR sciatica[TIAB]
#6 radiculopathy[TIAB] OR radiculitis[TIAB] OR radicular pain*[TIAB]
#7 (nerve root* adj5 (pain* OR avulsion OR compress* OR disorder* OR pinch* OR inflam* OR imping* OR irritat* OR entrap* OR trap*)) [TIAB]
#8 {or #6-#7}
#9 back*[TIAB] OR lumbosacral[TIAB] OR lumbo-sacral[TIAB] OR lumbar[TIAB]
#10 #8 and #9
#11 {or #1-#5, #10}
#12 Moxibustion/
#13 Artemisia/
#14 (moxibustion or moxabustion or moxa or artemisia or mugwort\$.tw.
#15 {or #12-#14}
#16 #11 and #15
#17 randomized controlled trial [PT]
#18 controlled clinical trial [PT]
#19 randomized [TIAB]
#20 placebo [TIAB]
#21 clinical trials as topic [mesh: noexp]

1
2
3
4 #22 randomly [TIAB]
5
6

7 #23 trial [TI]
8

9 #24 {or #17-#23}
10

11 #25 animals [mh] NOT humans [mh]
12

13 #26 #24 NOT #25
14

15 #27 #16 and #26
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21 [CENTRAL (cochrane) Search Strategy]
22

23 #1 MeSH descriptor: [Low Back Pain] explode all trees
24

25 #2 MeSH descriptor: [Sciatica] explode all trees
26

27 #3 MeSH descriptor: [Radiculopathy] explode all trees
28

29 #4 (lumbar or lumbosacral or lumbo-sacral or back) near/5 (pain* or ache* or
30
31
32 aching):ti,ab,kw (Word variations have been searched)
33

34 #5 backache* or lumbago or sciatica:ti,ab,kw (Word variations have been searched)
35

36 #6 radiculopathy or radiculitis or radicular pain*:ti,ab,kw (Word variations have been
37
38 searched)
39

40 #7 (nerve root* near/5 (pain* or avulsion or compress* or disorder* or pinch* or
41
42 inflam* or imping* or irritat* or entrap* or trap*)):ti,ab,kw (Word variations have been
43
44 searched)
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47 #8 {or #6-#7}
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49 #9 back* or lumbosacral or lumbo-sacral or lumbar:ti,ab,kw (Word variations have been
50
51 searched)
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54 #10 #8 and #9
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56 #11 {or #1-#5, #10}
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58 #12 MeSH descriptor: [Moxibustion] explode all trees
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4 #13 MeSH descriptor: [Artemisia] explode all trees
5
6 #14 moxibustion or moxabustion or moxa or artemisia or mugwort\$:ti,ab,kw (Word
7
8 variations have been searched)
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11 #15 {or #12-#14}

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13 #16 #11 and #15

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15 #17 (Select only trials)
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23 [EMBASE Search Strategy]
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28 #1 'Low Back Pain'/exp

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30 #2 'Sciatica'/exp

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32 #3 'Radiculopathy'/exp

33
34 #4 ((lumbar OR lumbosacral OR 'lumbo sacral' OR back) NEAR/5 (pain* OR ache* OR
35 aching)):ab,ti

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37 #5 (backache* or lumbago or sciatica):ab,ti

38
39 #6 (radiculopathy or radiculitis or radicular pain*):ab,ti

40
41 #7 (nerve root* NEAR/5 (pain* or avulsion or compress* or disorder* or pinch* or
42 inflam* or imping* or irritat* or entrap* or trap*)):ab,ti

43
44 #8 {or #6-#7}

45
46 #9 (back* or lumbosacral or lumbo-sacral or lumbar):ab,ti

47
48 #10 #8 and #9

49
50 #11 {or #1-#5, #10}

51
52 #12 Moxibustion/exp

53
54 #13 Artemisia/exp

55
56 #14 (moxibustion or moxabustion or moxa or artemisia or mugwort\$):ab,ti

57
58 #15 {or #12-#14}

59
60 #16 #11 and #15

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4
5 #17 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled
6 trial':de OR 'single-blind procedure':de OR (random* OR factorial* OR crossover* OR cross
7 NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR
8 assign* OR allocat* OR volunteer*):de,ab,ti
9

10 #18 #16 and #17
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14 [Chinese database search strategy : CNKI, VIP, Wanfang]
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18 #1 腰痛 and 灸
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20 #2 坐骨神经痛 and 灸
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22 #3 神经根型颈椎病 and 灸
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24 #4 腰椎 and 灸
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26 #5 腰骶部 and 灸
27

28 #6 背痛 and 灸
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30 #7 神经根炎 and 灸
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32 #8 神经根性疼痛 and 灸
33

34 #9 神经根 and 灸
35

36 #10 腰痛 and 艾
37

38 #11 坐骨神经痛 and 艾
39

40 #12 神经根型颈椎病 and 艾
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42 #13 腰椎 and 艾
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44 #14 腰骶部 and 艾
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46 #15 背痛 and 艾
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48 #16 神经根炎 and 艾
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50 #17 神经根性疼痛 and 艾
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5 #18 神经根 and 艾
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7 #19 腰痛 and 蒿
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10 #20 坐骨神经痛 and 蒿
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12 #21 神经根型颈椎病 and 蒿
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15 #22 腰椎 and 蒿
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18 #23 腰骶部 and 蒿
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20 #24 背痛 and 蒿
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22
23 #25 神经根炎 and 蒿
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25 #26 神经根性疼痛 and 蒿
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28 #27 神经根 and 蒿
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30 #28 or/#1-#27
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PRISMA- P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input type="checkbox"/>		1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			Not update for previous review
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input type="checkbox"/>		55
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input type="checkbox"/>		5-30
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input type="checkbox"/>		475-479
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments			Not amendment for previous review
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input type="checkbox"/>		468-470
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>		468-470
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol			No roles exist
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input type="checkbox"/>		96-130

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input type="checkbox"/>		133-136
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input type="checkbox"/>		148-197
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input type="checkbox"/>		199-214
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input type="checkbox"/>		199-214
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input type="checkbox"/>		222-240
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input type="checkbox"/>		223-229
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input type="checkbox"/>		231-240
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input type="checkbox"/>		231-240
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input type="checkbox"/>		176-197
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input type="checkbox"/>		242-251
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>		291-301
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input type="checkbox"/>		279-301

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input type="checkbox"/>		303-321
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>		291-301
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input type="checkbox"/>		274-277
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>		291-301

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