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Review | Revisión

Efficacy, safety and tolerability of Tiger Balm® ointments: a systematic review and a meta-analysis of prevalence

[Eficacia, seguridad y tolerabilidad de los ungüentos Tiger Balm®: una revisión sistemática y un metanálisis de prevalencia]

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Abstract

Context: Tiger Balm® (TB®) ointments are multi-purpose branded Chinese topical remedies, often used for pain relief and purchasable in many countries as over-the-counter medications.

Aims: To assess the efficacy, safety and tolerability of TB® ointments.

Methods: Medline, Scopus, EMBASE, Cochrane Library, Web of Science, Google Scholar, PEDro, and the Chinese Clinical Trial Registry were systematically searched for relevant articles. The quality of included studies on the efficacy of TB® ointments was evaluated with dedicated NIH tools. Retrieved evidence was then summarized and critically appraised.

Results: After article screening and selection, 12 studies were finally included in the present review (five on TB® ointments efficacy, whereas seven on their safety and tolerability). Two cases of dermatitis and one of cheilitis likely ascribable to the use of TB® ointments have been reported. Based on available studies, it might be estimated that around 4% [95% CI, 3%-5%] of patients with history of contact skin allergy could be positive if patch tested with TB® ointments, therefore caution is recommended in the use of TB® among these subjects.

Conclusions: According to retrieved evidence, TB® ointments might be useful for the management of pain due to tension headache, and they seem capable of increasing leg blood flow if combined with massage. Considering available evidence on topical products with camphor, TB® ointments shouldn't be used in children, as well as in pregnant or lactating women. Chronic use, large amounts of balm, and the application on damaged skin must be avoided too. Further studies are recommended.

Keywords: drug efficacy; drug safety; systematic review; traditional Chinese medicine.

Resumen

Contexto: Los ungüentos Tiger Balm® (TB®) son remedios tópicos chinos de marca multipropósito, a menudo utilizados para aliviar el dolor y que se pueden comprar en muchos países como medicamentos de venta libre.

Objetivos: Evaluar la eficacia, seguridad y tolerabilidad de los ungüentos TB®.

Métodos: Se realizaron búsquedas sistemáticas de artículos relevantes en Medline, Scopus, EMBASE, Cochrane Library, Web of Science, Google Scholar, PEDro y el Registro de ensayos clínicos chinos. La calidad de los estudios incluidos sobre la eficacia de los ungüentos TB® se evaluó con herramientas NIH dedicadas. La evidencia recuperada se resumió y se evaluó críticamente.

Resultados: Después del tamizaje y selección del artículo, finalmente se incluyeron 12 estudios en la presente revisión (cinco sobre la eficacia de los ungüentos TB®, mientras que siete sobre su seguridad y tolerabilidad). Se han informado dos casos de dermatitis y uno de queilitis probablemente atribuibles al uso de ungüentos TB®. Según los estudios disponibles, se podría estimar que alrededor del 4% [IC 95%, 3% -5%] de los pacientes con antecedentes de alergia cutánea por contacto podrían ser positivos si el parche se prueba con ungüentos TB®, por lo tanto, se recomienda precaución en el uso de TB® entre estos sujetos.

Conclusiones: Según la evidencia recuperada, los ungüentos TB® podrían ser útiles para el tratamiento del dolor debido al dolor de cabeza por tensión, y parecen capaces de aumentar el flujo sanguíneo de las piernas si se combinan con un masaje. Teniendo en cuenta la evidencia disponible sobre productos tópicos con alcanfor, los ungüentos TB® no deben usarse en niños, así como en mujeres embarazadas o lactantes. También se debe evitar el uso crónico, grandes cantidades de bálsamo y la aplicación sobre la piel dañada. Se recomiendan más estudios.

Palabras Clave: eficacia del fármaco; medicina tradicional china; revisión sistemática; seguridad de drogas.

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INTRODUCTION

Tiger Balm® (TB®) ointments are Chinese multi-purpose topical products, often used for pain relief and available in many countries as over-the-counter herbal remedies (The Tiger Balm Philosophy, 2014). TB® ointments are today produced by an Asian company based in Singapore and they are claimed to be invented decades ago by a Chinese herbalist named Aw Chu Kin (The Tiger Balm Philosophy, 2014). Their traditional uses include symptomatic relief for pain associated with muscular ache, arthritis, and rheumatism (A. Aldulaimi and Li, 2016). Moreover, in the East, TB® ointments are applied on the chest as a balsam for respiratory ailments like bronchial inflammation or asthma (Fan, 2009).

In the United Kingdom, two traditional ointment formulations of TB® are Red TB® and White TB® (Shih et al., 2015). Red TB® is recommended by the producer to soothe sore and aching muscles, and it is reported to contain camphor (11.0%), menthol (10.0%), clove oil (5.0%), cajuput oil (7.0%), as well as cinnamon oil, dementholized mint oil, yellow soft paraffin and hard paraffin (Tiger Balm Red, 2014). White TB® is recommended by the producer to relieve pain of tension headaches, and it is reported to contain camphor (11.0%), menthol (8.0%), clove oil (1.5%), cajuput oil (13.0%), as well as dementholized mint oil, yellow soft paraffin and hard paraffin (Tiger Balm White, 2014). Overall, according to disclosed information about composition of these two formulations, Red TB® has a higher concentration of clove oil and menthol, a lower concentration of cajuput oil, and contains cinnamon oil (Tiger Balm Red, 2014; Tiger Balm White, 2014). Red TB® has been also analyzed with gas chromatographic techniques by some researchers, showing a relative abundance of camphor and menthol, which should be considered the characteristic chemical markers of this herbal remedy (A. Aldulaimi and Li, 2016). Some formulations other than Red or White TB® ointments (like the liquid TB® liniment) have been reported to contain compounds like methyl salicylate (Davis, 2007).

According to the definition of the National Cancer Institute (NCI), Complementary and Alternative Medicines (CAM) are forms of treatment that are used in addition to (complementary) or instead of (alternative) standard treatments, and these practices are not generally considered standard medical approaches (NCI Dictionary of Cancer Terms, 2011). Therefore, TB® ointments, being a traditional herbal preparation, can be classified as a CAM remedy (2011). Patients with pain, including musculoskeletal pain (which appears to be one of the most important indications of TB® ointments), are reported to likely use CAM treatments (Artus et al., 2007; Tan et al., 2013). This tendency has also been confirmed for patients already taking analgesic drugs (like opioids) for pain management (Fleming et al. 2007). In fact, in a survey of 1259 CAM users with knee osteoarthritis, it was reported that 352 (28.0%) of them used topical agents like TB® ointments (Lapane et al., 2012). As over-the counter products, TB® ointments can be purchased by patients without any medical prescription. Moreover, TB® ointments are not only used by adults, but, in countries like Cambodia, even children and infants are reported to be given this remedy for colicky pain or other pain-related problems (Johnson et al. 2017). Therefore, due to their worldwide availability and use, it is important to evaluate whether TB® ointments have some demonstrated therapeutic effects, and if they can be considered a safe and well-tolerated remedy in the light of existing scientific evidence on the topic.

The aim of this systematic review is to assess the clinical efficacy, safety and tolerability of TB® ointments.

MATERIAL AND METHODS

The PRISMA guidelines were followed for the present review (Moher et al., 2015).

Eligibility and exclusion criteria (PICOS)

All studies investigating the clinical efficacy, safety and tolerability of TB® ointments both in healthy subjects and in patients with a diagnosed

disease were included. Intervention was defined as the topical administration of TB® ointments, applied over the skin with or without massage. All studies were included regardless of comparison/control group type. All clinical outcomes were considered, including any change in disease severity, physiological parameters, subjective symptoms, and reported quality of life. No language restrictions were applied during article selection process.

The following list summarizes the applied PICOS criteria for inclusion and exclusion of studies in the present review:

- **P** (Population): healthy subjects or patients with a diagnosed disease.
- **I** (Intervention): topical administration of TB® ointments.
- **C** (Comparison): any type of comparison (placebo, usual care, other treatments, or no control).
- **O** (Outcomes): any change in disease severity, physiological parameters, subjective symptoms, and reported quality of life.
- **S** (Study design): all types of study design.

Information sources

Medline via PubMed, Scopus, EMBASE, Cochrane Library, Web of Science, Google Scholar, PEDro, and the Chinese Clinical Trial Registry were systematically searched for relevant studies investigating the clinical efficacy, safety and tolerability of TB® ointments both in healthy subjects and in patients with a diagnosed disease.

Search

Databases were searched up to February 2nd, 2019. The following search strategies were used (see Table 1 for a brief summary of keywords and results obtained after searching each database):

Table 1. Keywords and results of searches conducted in each database.

Database	Keyword(s)	Item(s) searched
PubMed	"tiger balm" OR "tiger balsam" OR "tiger oil" OR "camphor balm" OR "menthol balm"	8
Scopus	"tiger balm" OR "tiger balsam" OR "camphor balm" OR "menthol balm"	23
EMBASE	"tiger balm" OR "camphor balm" OR "menthol balm"	12
Cochrane Library	"tiger balm"	1
Web of Science	"tiger balm" OR "camphor balm" OR "menthol balm"	5
Google Scholar	"tiger balm" AND "trial" "tiger balm" "camphor balm" "menthol balm" "tiger oil" "tiger balsam"	474 12 31 289 30
Chinese Clinical Trial Registry	"tiger balm"	0
PEDro	"tiger balm"	1

Study selection and data collection process

Study screening and selection was performed by two authors independently. Afterwards, disagreements were discussed until consensus was reached. Details of study selection and data collection process were summarized in a flowchart (Fig. 1) (Moher et al. 2015). Data were manually extracted from included articles, collected in tables and then critically appraised. When data were missing, authors were contacted by email to recover essential information. The full-text version of an article was retrieved in this way (Schattner and Randerson, 1996).

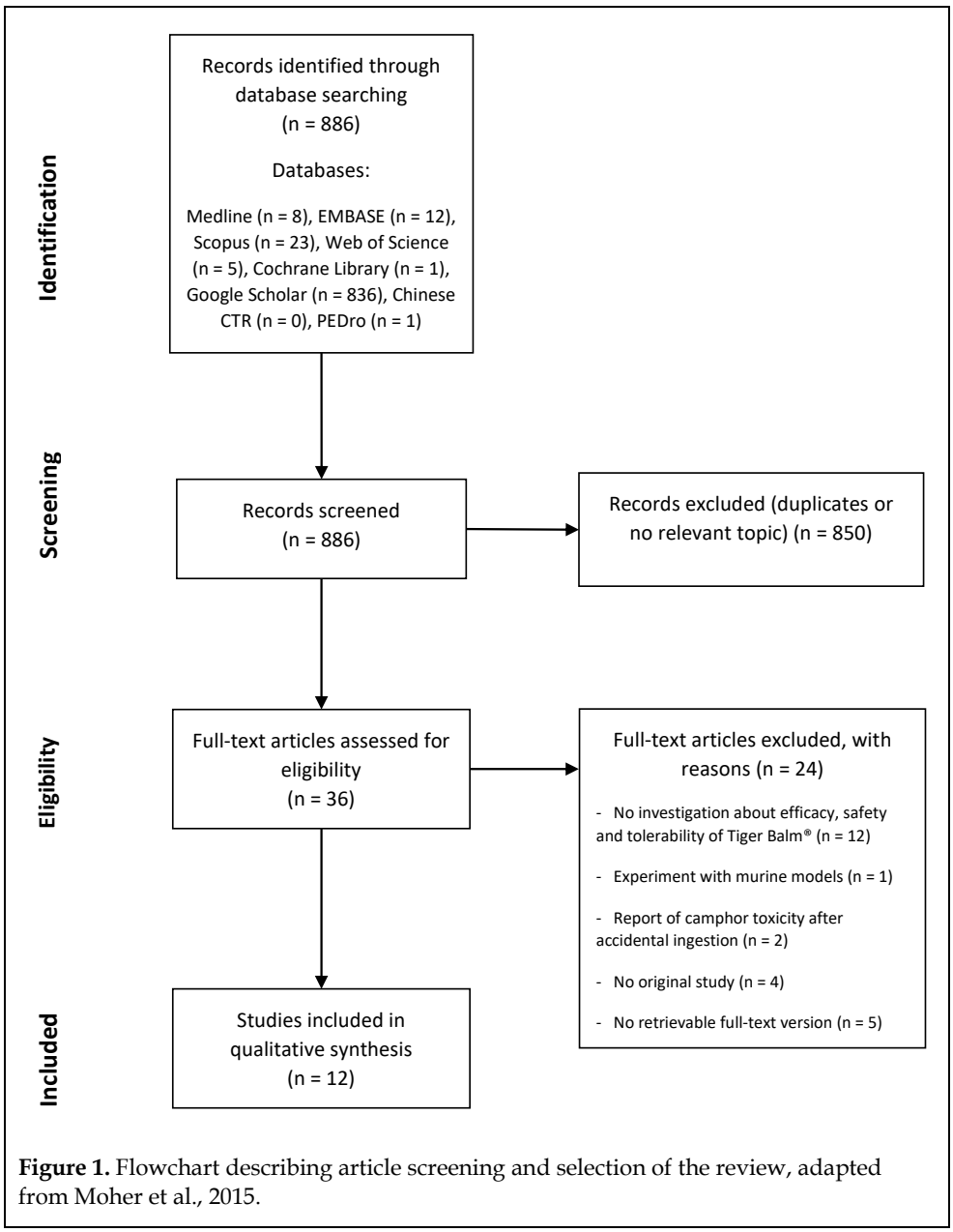

Figure 1. Flowchart describing article screening and selection of the review, adapted from Moher et al., 2015.

Data items

Data items extracted from included reviews were the following ones: characteristics of the study population and intervention, comparison type and analyzed outcomes, study design, the overall results and the authors' conclusions.

Risk of bias in individual studies and across studies

A dedicated tool developed by the National Institutes of Health (NIH) was used for the quality assessment of controlled intervention studies (Study Quality Assessment Tools – NHLBI, 2018).

The overall evaluation was based on the answers to 14 questions, regarding the presence and methods of randomization, the treatment allocation concealment, the blinding of study participants and outcome assessors, the absence of significant differences between groups at baseline, the attrition and dropout rate, the adherence to intervention protocol, the presence of confounding factors, the use of valid and reliable measures, the recruitment of a sufficient number of participants, and other potential sources of bias. Every question could be answered in three ways, either "yes", or "no", or "other" (which indicates that data are not reported, the answer cannot be determined, or the question is not applicable). Studies were assessed individually and their overall quality was scored as poor if 6 or less of the items were positive (answered with "yes"), fair if positive items ranged from 7 to 9, and good if at least 10 items were positive. When items couldn't be determined, were not applicable, or were not reported, the overall quality was decided on the basis of available data.

Another dedicated NIH tool was used for the quality assessment of pre-post studies with no control group (Study Quality Assessment Tools – NHLBI, 2018). The overall evaluation was based on the answers to 12 questions, regarding the clarity of study objectives, eligibility criteria of participants and tested intervention, the validity and reliability of outcome measures, the recruitment of a sufficient number of participants, the blinding of study outcome assessors, the attrition and dropout rate, the appropriateness of statistical methods used to analyze data, and other potential sources of bias. Every question could be answered in three ways, either "yes", or "no", or "other" (which indicates that data are not reported, the answer cannot be determined, or the question is not applicable). Studies were assessed individually, and their overall quality was scored as poor if 4 or less of the items were positive (answered with "yes"), fair if positive items ranged from 5 to 7, and good if at least 8 items were positive. When items couldn't be determined, were not applicable, or were not reported, the overall quality was decided on the basis of available data.

Quality of evidence from case reports and case series describing potential side effects of TB® were assessed with another tool, recently developed by synthetizing and adapting to these study types several already existing evaluating criteria, including the Newcastle Ottawa scale (Murad et al., 2018). This tool covers four domains (selection, ascertainment, causality, and reporting), described in eight items. The overall score ranges from 0 to 8, with 8 representing the highest possible quality.

Results of the overall quality assessment were reported in a specific column of Tables 2 and 3.

Summary of measures and synthesis of results

Results were summarized in two tables: Table 2, reporting characteristics and quality of included studies analyzing the efficacy of TB® ointments, and Tables 3 and 4, reporting information from the most relevant case reports or case series, and observational studies about the safety and tolerability of TB® ointments. Then, retrieved evidence was discussed to obtain a critical qualitative synthesis.

Among included studies investigating TB® ointments tolerability with patch tests (Bruze et al., 1999), prevalence data from those ones involving patients (at least 20 subjects) with history of (or with a suspected) allergic contact dermatitis to any substance other than TB® products were extracted. A meta-analysis of prevalence was therefore performed, using the "MetaXL" software (version 5.3) (Barendregt et al., 2013). Prevalence was considered as the ratio between the number of patients who were positive when patch tested with TB® ointments and the total number of analyzed patients. The inverse variance method was adopted to obtain individual study weight and pooled prevalence. The double arcsine transformation was applied, and preferred over the logit transformation, to stabilize the variance (Barendregt et al., 2013). Results of this analysis were reported in dedicated plots (Fig. 2).

Table 2. Characteristics and quality of included studies on the efficacy of Tiger Balm®.

Reference	Population	Intervention	Comparison(s)	Outcome(s)	Study design	Quality	Main results (quotation)	Authors' conclusions
Schattner & Randerson, 1996	57 patients with acute tension headache (22 males; age range: 18-60 years): TB® group (n=22), placebo group (n=20), drug group (n=22).	Application (rubbing) of TB® onto the temple three times (at baseline, after 30 min and 1 h).	Yes (paracetamol 1000 mg or placebo topical treatment)	Headache severity (scale 0-7) and relief (scale 0-4) measured 5, 15, 30, 60, 120, and 180 min after intervention.	RCT	A	Statistical analysis shower that Tiger Balm® is significantly different to placebo from 5 min to 2 h. Tiger Balm® and paracetamol groups recorded a significant decline in headache severity during the 3 h period, although Tiger Balm® was found to provide more rapid relief than paracetamol at 5 and 15 min.	Positive, in favor of the efficacy of TB®.
Case et al., 2013	54 healthy subjects (19 males, mean age: 20.9 ± 2.13): 3 groups (n=18 in each group).	Application of TB® on the left cheek.	Yes (moisturizing cream or anesthetic cream)	Measures of sensory referral (touch-confusions, subjective tingliness, and sensory acuity).	RCT	A	[TB®] caused higher ratings of tingliness than numbing cream or moisturizer. The three conditions did not differ significantly in participants' estimated sensory acuity in the cream region. [TB®] and moisturizer did not differ significantly in the number of touch-confusions observed.	NA*
Ljungfelt et al., 1994	12 healthy subjects (4 males; age range: 16-48 years, mean age: 26.4).	Massage with TB® and Frisco® liniment of lower limbs (TB® on one leg, Frisco® on the other one).	Yes (the same liniments applied with a stick)	Blood flow in lower limbs measured with strain-gauge plethysmography and laser Doppler flowmetry.	Cross-over non-RCT	B	Tiger Balm® with massage increased the skin blood flow by 20.4 ± 8.0 perfusion units, "immediately after". The increase was significant for 40 min. Stick application of Tiger Balm® gave a slow increase in skin blood flow and was significant after 50 min. Massage with Tiger Balm® increased the calf blood flow by 2.2 ± 0.8 mL/min/100 mL tissue "immediately after". The increased blood flow was significant even after 60 min. Stick application of Tiger Balm® did not influence the calf blood flow.	Positive, in favor of the efficacy of TB®.
Li et al., 2009	45 patients with headache caused by cold (sex ratio and mean age: unknown).	Application of essential balm or TB®, or warm water on specific areas of the body, mostly using a spoon (chest, back, bilateral Taiyang (Ex-HN 5), Yintang (Ex-HN 3).	No	VAS (pain)	Pre-post US	C	The VAS score of pre-treatment was 6.45 ± 1.95 and it was 1.43±0.65 after treatment.	Positive, in favor of the efficacy of massage with or without TB®.
Fan, 2009	38 patients with bronchial asthma (sex ratio: unknown; average age: 47.4 ± 8.3 years).	Application of essential balm or TB®, or warm water on specific areas of the body, using a spoon (upper back, along the pathway of Bladder Meridian), every 10-20 days for 3 years.	No	The patient's average frequency of asthma attack (recorded once every 6 months for 3 years).	Pre-post US	C	The average annual frequency of asthma attack prior to the scraping method was (2.3 ± 1.3) times, and (0.6±0.4) times after the scraping treatment.	Positive, in favor of the efficacy of massage with or without TB®.

NA = Not Applicable, RCT = Randomized Controlled Trial, TB® = Tiger Balm®, US = Uncontrolled Study. Studies are listed according to their design, with priority for controlled trials. PICOS characteristics of each included study are briefly reported in the table, as well as the quality of their evidence (A = good, B = fair, C = poor), and a quotation from original texts summarizing the main findings. Threshold for significance was considered at $p<0.05$. The last column reports the authors' conclusions on the topic.
*The aim of this study was not to assess the therapeutic efficacy of TB®, but to use it as a control in order to comparatively test the effects of a lidocaine-based cream on sensory referral in healthy participants completing an experimental task.

Table 3. Case reports about side effects of Tiger Balm®.

Reference	Case N°	Gender	Age	Health condition	Anamnesis and additional information	Quality
Leow et al., 1995	1	F	52	12-year history of recurrent cheilitis.	History of using Tiger Balm®. Positive Patch Test.	4/8
Schliemann et al., 2011	2	M	48	Itching, erythema, and scaling on the forehead.	History of using Tiger Balm®. Positive Patch Test. Evidence of hay fever and mild atopic skin diathesis.	6/8
	3	F	36	Severe contact dermatitis on the back.	History of using Tiger Balm®. Positive Patch Test. No history of cosmetic or fragrance allergy, and no atopy.	6/8

F = Female; M = Male. This table summarizes case reports about side effects of Tiger Balm®.

Table 4. Studies investigating the prevalence of contact allergy to Tiger Balm®.

Reference	Type of TB® (% of agent in vehicle)	Time after record of test results	Number of positive subjects	Number of tested subjects	% (N of positive/tested subjects)	Characteristics of study population
Anggraini et al., 2017	NA	NA	1	1	100.0%	Patients with allergic contact dermatitis and with a positive result for at least one allergen.
Lee & Lam, 1990	Red TB®	48 h	2	20	10.0%	Patients with eczema or contact dermatitis due to substances other than TB®.
		96 h	1	17	5.8%	
Leow et al., 1995	White TB® (1%)	NA	0	12	0.0%	Patients with history of dermatitis of a likely contact origin, not related to the usage of topical traditional Chinese medicaments and patients with a primary dermatitis under control.
	White TB® (5%)		1	22	4.5%	
	White TB® (10%)		3	55	5.5%	
Leow, 1997	NA	NA	0	87	0.0%	Subjects with no history of allergic contact dermatitis, probably healthy (reported as "controls").
Lim et al., 2007	White TB® (10%)	48-72-168 h	3	44	6.8%	Patients with chronic venous (or mixed venous and arterial) leg ulcers.
Schliemann et al., 2011	Red TB®	NA	7	18	38.9%	Patients with concomitant reactions to other fragrances.
Shih et al., 2015	Red TB®	48-72-96 h	42	1076	3.9%	Patients with suspected allergic contact dermatitis.
	White TB®	48-72-96 h	39	1076	3.6%	

NA = Not Available, TB® = Tiger Balm®. This table summarizes data of studies investigating tested contact allergy to Tiger Balm®. Articles are alphabetically sorted according to the first author's surname.

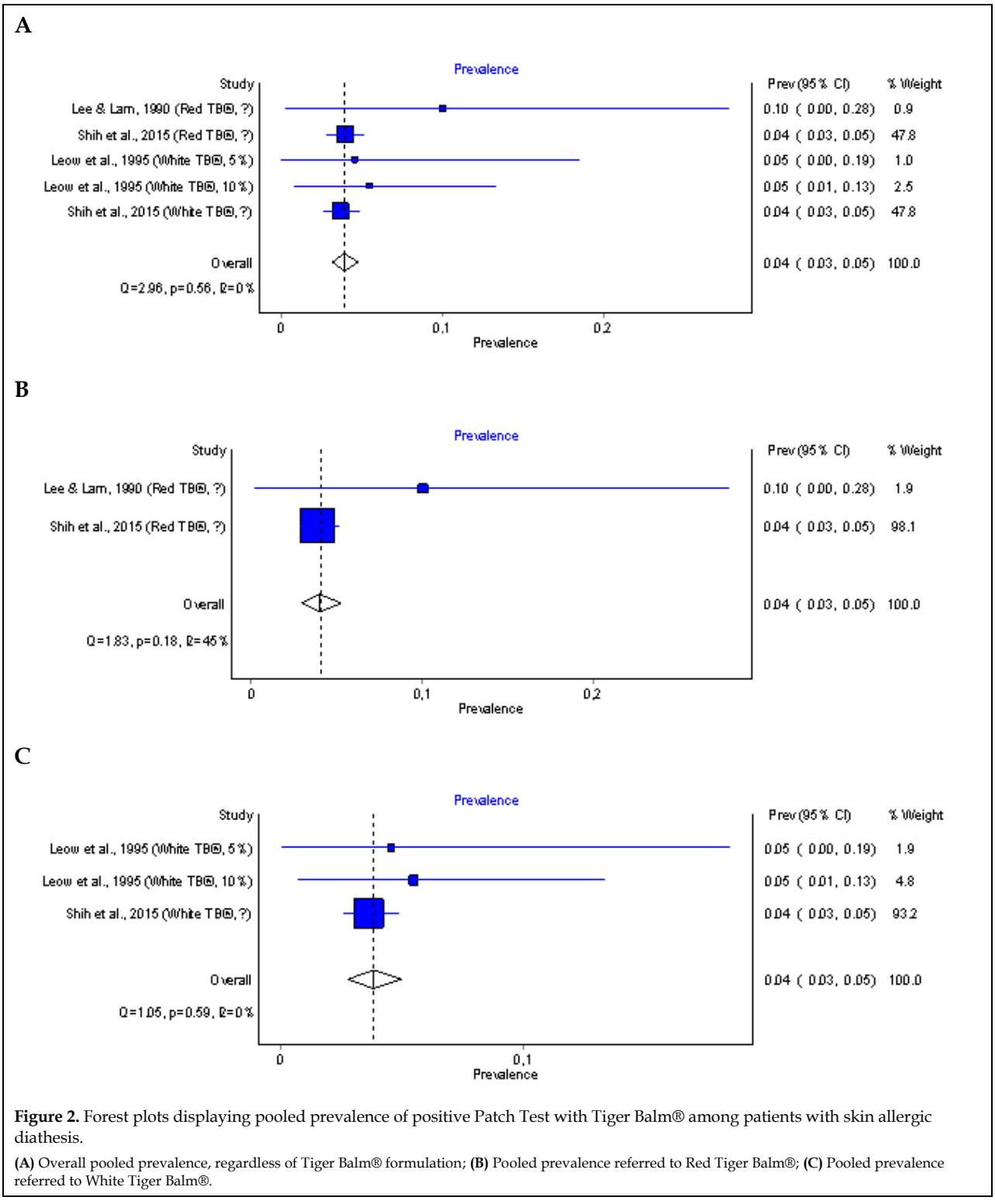

Figure 2. Forest plots displaying pooled prevalence of positive Patch Test with Tiger Balm® among patients with skin allergic diathesis.

(A) Overall pooled prevalence, regardless of Tiger Balm® formulation; **(B)** Pooled prevalence referred to Red Tiger Balm®; **(C)** Pooled prevalence referred to White Tiger Balm®.

RESULTS

After database searching, 886 articles were screened and twelve of them were finally included in the review. Among them, five articles investigated TB® ointments efficacy (Ljungfelt et al., 1994; Schattner and Randerson, 1996; Fan, 2009; Li, et al. 2009; Case et al., 2013), while seven of them

reported information about their safety and tolerability (Lee and Lam, 1990; Leow et al., 1995; Leow, 1997; Lim et al., 2007; Schliemann et al., 2011; Shih et al., 2015; Anggraini et al., 2017), as displayed in each table (Tables 2-4). Details of article screening and selection process was described in a flowchart (Fig. 1).

Five articles investigated the therapeutic efficacy of TB® ointments and their physiological effects. In an included Randomized Controlled Trial (RCT), authors reported that the efficacy of TB® (unspecified formula, but probably White TB® ointment) in relieving pain due to acute tension headache was significantly better than a topical placebo remedy ($p<0.05$) and was found to provide more rapid relief than a single dose (1000 mg) of paracetamol (Schattner and Randerson, 1996). In a physiological study about the effects of two topical products on leg circulation, TB® (unspecified formula) was reported to increase the skin and calf blood flow in combination with massage ($p<0.05$) (Ljungfelt et al., 1994). In another study, TB® (White formula ointment) was used as a control intervention to comparatively test the effects of a lidocaine-based cream on sensory referral in healthy participants performing an experimental task (Case et al., 2013). Reported outcomes were touch-confusions (participants saying both sides when the touching stimulus was applied only on one side), subjective tingling (rated by the participants using a 0-5 scale), and sensory acuity (rated by the participants using a 0-100 scale) (Case et al., 2013). Results of this double-blind RCT showed that TB®, when applied over face skin, seems capable of inducing a tingling sensation which appears significantly more pronounced than that one caused by the application of the anesthetic cream ($p<0.01$), without impairing the subjects' estimated sensory acuity more than a placebo moisturizing cream ($p=0.261$) (Case et al., 2013). Moreover, TB® and moisturizer did not differ significantly in the number of touch-confusions observed ($p=0.27$) (Case et al., 2013). In two pre-post uncontrolled studies, topical applications of TB® ointments (unspecified formula), another balm or warm water were used as a remedy for cold-related headache, reporting a significant improvement in perceived pain ($p<0.05$) (Li et al., 2009), and for bronchial asthma, reporting a significant decrease in average annual frequency of asthma attacks ($p<0.05$) (Fan, 2009). The quality of included studies, assessed with dedicated NIH tools, was rated as good for two studies (Schattner and Randerson, 1996; Case et al., 2013), fair for another one (Ljungfelt et al., 1994), while poor for the remaining two (Fan, 2009; Li et al., 2009).

Two articles described three cases of patients using TB® ointments and reporting adverse events probably ascribable to its skin application (Leow et al., 1995; Schliemann et al., 2011). One article described a case report regarding a 48-year-old man with itching erythema on his forehead, and another one regarding a 36-year-old woman experiencing severe dermatitis on her back (Schliemann et al., 2011). Both cases reported a history of TB® use on skin regions involved by contact dermatitis and were positive when patch tested with TB® (Schliemann et al., 2011). In another article a 52-year-old woman with a history of cheilitis reported the use of TB® and showed a positive reaction when patch tested with TB® (Leow et al., 1995). Quality of these case reports ranged from 4 to 6 out of 8, with 8 representing the highest quality (Leow et al., 1995; Schliemann et al., 2011).

Seven articles reported cases of people who exhibited a positive response after being patch tested with TB® ointments to check whether they showed any contact allergy (Table 4) to these herbal remedies (Lee and Lam, 1990; Leow et al., 1995; Leow, 1997; Lim et al., 2007; Schliemann et al., 2011; Shih et al., 2015; Anggraini et al., 2017). Results of these studies were highly heterogeneous, with a number of included participants ranging from 1 to 1076 (median: 22), and a percentage ratio between the number of positive subjects and the number of tested ones ranging from 0.0% to 100.0% (median: 5.5%) (Lee and Lam, 1990; Leow et al., 1995; Leow, 1997; Lim et al., 2007; Schliemann et al., 2011; Shih et al., 2015; Anggraini et al., 2017). In all but one study (Leow, 1997), tested participants were patients with history of dermatologic or allergic diseases, mostly allergic contact dermatitis. If studies with less than 20 subjects are excluded and only those ones involving patients

with history of (or with a suspected) allergic contact dermatitis to any substance other than TB® are taken into account, pooled prevalence of patients who were positive when patch tested with TB® was 4% [95% CI, 3%-5%] (Fig. 2). This prevalence remained the same when Red and White TB® ointments were considered separately (Fig. 2).

DISCUSSION

Efficacy

In one RCT on TB®, its efficacy in relieving pain due to acute tension headache was tested in comparison with paracetamol (administered at a single dose of 1000 mg), and a placebo topical ointment (Schattner and Randerson, 1996). When critically appraising evidence from this RCT, it has to be acknowledged that baseline characteristics of patients assigned to placebo and intervention groups had some heterogeneity in terms of reported headache frequency and duration, with a tendency towards higher average frequency and longer average disease duration in subjects assigned to the placebo group (Schattner and Randerson, 1996). Moreover, the authors recognized that the sample size was limited, since a power calculation based on the hypothesis that the difference in severity between groups was at worst one unit, demonstrated that 44 patients were required in each group (around half of those ones actually recruited) (Schattner and Randerson, 1996). However, considering the overall high quality of this trial and the significance of its findings, it can be concluded that TB® ointment massaged on the temple may be a useful remedy for pain relief in this condition on a short term. Moreover, in a double-blind RCT investigating the effects on tension-type headache of a locally applied preparation with peppermint oil (one of the chemical markers of TB®), the remedy was discovered to significantly reduce the headache intensity if compared to placebo ($p<0.01$) (Göbel et al., 1996). The effect continued over the one-hour observation period and was found to be comparable to the oral intake of 1000 mg of paracetamol (Göbel et al., 1996). Coupling paracetamol and peppermint oil application led to an additive, although not statistically significant, effect (Göbel et al., 1996). In another RCT with a crossover design involving 32 subjects with headache, pain was significantly reduced by applying on the forehead and temples a combination of peppermint oil and ethanol, thus underscoring the potentially beneficial effects of peppermint-based topical products in relieving cefalalgic symptoms (Göbel et al., 1994). Additionally, a study involving 60 patients with mechanical neck pain showed that a topically applied menthol gel can significantly reduce reported pain ($p<0.05$), although a non-significant effect was found in terms of changes in neck range of motion (Topp et al., 2017). In a randomized trial with 40 patients affected by either chronic neck pain or chronic low back pain, significant improvements in health status and pain ($p<0.05$) were reported in the group treated with "Gua Sha" therapy, compared to the waiting list group (Lauche et al., 2012). "Gua Sha" therapy was defined as an instrument-assisted massage of an area of the body surface lubricated with a balm containing camphor, menthol, and eucalypt (Lauche et al., 2012). Evidence from all these studies seems to suggest that topical products containing camphor, menthol or peppermint oil might be useful for the management of pain due to muscular tension.

In a physiological study about the effects of two topical products on leg circulation, TB® was reported to increase the skin and calf blood flow in combination with massage ($p<0.05$) (Ljungfelt et al., 1994). Similar findings have been reported in a study with nine participants in which it was demonstrated that the application of a topical preparation containing camphor or menthol on the forearm can increase skin and muscle blood circulation (Kotaka et al. 2014).

Two other studies on TB® ointments therapeutic effects were performed in China and aimed to investigate the efficacy of Chinese massage techniques in relieving symptoms of headache caused by cold or relapses of chronic asthma (Fan, 2009; Li et al., 2009). In both studies, intervention was administered by domestic caregivers and family members, who had the opportunity to choose among a range of three topical therapeutic options, including TB® (Fan, 2009; Li et al., 2009). There-

fore, since no detailed information is provided, it cannot be argued how many patients were actually given a TB® ointment as a remedy. Moreover, these studies simply assessed pre-post outcome variations in a relatively small population, thus lacking any type of comparison or control group (Fan, 2009; Li et al., 2009). Finally, due to the limited information provided about the nature of intervention, confounding factors might have biased study results.

Mechanisms of action

Among all compounds included in TB® ointments, the most active ones from a pharmacological point of view are considered camphor, menthol, cajuput, mint oil, clove oil, and cinnamon oil (Faubert et al., 2010). However, the characteristic chemical markers of this herbal remedy are mainly considered camphor and menthol (A. Aldulaimi and Li, 2016). Some formulations other than Red or White TB® ointments (like the liquid TB® liniment) have been reported to contain methyl salicylate, an aspirin-like compound which is a component of many over-the-counter topical remedies used for musculoskeletal aches and pain (Davis, 2007).

Camphor (usually extracted from *Cinnamomum camphora*) has been hypothesized to have several biological properties, including antimicrobial, antitussive and anti-nociceptive activities (Chen et al., 2013b). It is supposed that the analgesic effects of camphor may be due to a de-sensitization of TRPV1 (vanilloid receptor 1) and a blocking of TRPA1 (transient receptor potential ankyrin 1) (Chen et al., 2013b). Moreover, camphor can activate and sensitize TRPM8 (transient receptor potential melastatin 8) with a dual and complex action (stimulating the receptor while inhibiting its response to menthol), and this mechanism is likely to be responsible for the enhancement of cold sensations by camphor (Selescu et al., 2013). Camphor can also induce an agonist-specific desensitization of TRPV3 (transient receptor potential vanilloid-3 ion channels), which has a specific role in thermosensation and nociception (Moqrich et al., 2005; Sherkheli et al., 2009). Skin penetration enhancement properties have been hypothesized to depend on terpenes contained in camphor essential oil (Chen et al., 2013a). A study with murine models has also reported that a combination of menthol and camphor, both present in TB®, can enhance skin penetration of methyl salicylate and inhibit its hydrolysis to salicylic acid (Yano et al., 1991).

Menthol, a cyclic terpene alcohol found in mint (*Mentha* spp.), can stimulate TRP (transient receptor potential) ion channels and, although irritating and noxious at high doses, this compound can cause a pleasing sensation of cold when used in moderate concentrations (Liedtke, 2006; Bautista et al., 2007). Studies in vitro and in vivo have highlighted the anti-nociceptive and muscle-release effects of menthol, probably mediated by its action on receptors like the TRPM8, as well as on neuronal and skeletal muscle sodium channels (Haeseler et al., 2002; Nomoto et al., 2008). Menthol has also a bimodal action on the TRPA1, characterized by the activation of this receptor at submicromolar doses and inhibition at higher concentrations (Karashima et al., 2007), and may be capable of desensitizing the TRPV3 (Sherkheli et al., 2009). Menthol inhalation can also reduce cough sensitivity to inhaled capsaicin and positively influence inspiratory flows (Millqvist et al., 2013).

Clove oil is traditionally obtained from *Eugenia caryophyllata* and its major component is considered to be eugenol (Chaieb et al., 2007). In a review of the scientific literature, clove oil has been reported to potentially have several properties, including antimicrobial, antioxidant, and analgesic effects (Chaieb et al., 2007). In a study with mice, the anti-nociceptive activity of eugenol was demonstrated with various experimentally induced pain models (Bodhankar et al., 2006). Eugenol can activate TRP channels, in particular A1, V1, V3, and M8 receptors, thus modulating sensory neuronal responses to warmth and noxious stimuli (Klein et al., 2013;2014; Chung et al., 2014).

Cajuput oil is produced with *Melaleuca cajuputi* and it is considered a popular household medication in countries such as India, Indonesia, Malaysia and Vietnam, as well as among Australian Aborigines, mostly for the treatment of aches and

pains, and to reduce nasal and bronchial congestion (Doran, 2003). Cajuput oil can contain 40-70% of 1,8-cineole, active on M8, A1, and V3 TRP receptors, with possible anti-inflammatory and antinociceptive effects (Sherkheli et al., 2009; Caceres et al., 2017).

Cinnamon oil is extracted from *Cinnamomum zeylanicum* and, in a cellular model of chronic inflammation and fibrosis, has showed an anti-inflammatory activity mediated by the inhibition of the production of several inflammatory biomarkers (such as vascular cell adhesion molecule-1, intercellular cell adhesion molecule-1, monocyte chemoattractant protein-1, interferon gamma-induced protein 10, interferon-inducible T-cell alpha chemoattractant, and monokine induced by gamma interferon), and of some tissue remodeling molecules (like epidermal growth factor receptor, matrix metalloproteinase-1, and plasminogen activator inhibitor-1) (Han and Parker, 2017). Moreover, cinnamaldehyde from cinnamon bark oil can activate the TRPA1, which has a role in modulating nociception and inflammation (Mendes et al., 2016), and it might also modulate other thermos-TRPs like TRPV3 (Macpherson et al., 2006).

Another compound present in TB® ointments is paraffin (TIGER BALM RED; TIGER BALM WHITE), which can have a role as a skin penetration enhancer (Chen et al., 2013a) and as a skin-protective material against contact irritants and allergens (Zhai et al., 1998), thus promoting the absorption of active substances contained in the balm and potentially limiting possible irritation caused by other constituents of the ointment.

Methyl salicylate (not contained in Red or White TB® ointments, but in other formulations like the liquid TB® liniment) is an important component of many rubefacients, namely topical remedies used for muscular pain, which can cause skin reddening and irritation by dilating blood vessels and stimulating peripheral nerves (Derry et al., 2014). Although chemically related to aspirin and other non-steroidal analgesic drugs, the mechanism of action of methyl salicylate is not completely clear, even if the most relevant hypothesis is that it could work by counter-irritation, thus giving a soothing feeling of warmth and a pain relief effect in the underlying muscle (Derry et al., 2014). It is possible to hypothesize that the counter-irritation effect of methyl salicylate may be due to its activity on TRPA1 and V1, thus inducing a local cutaneous neurogenic inflammation (Gouin et al., 2017). The real efficacy of topical methyl salicylate-based products in the management of acute and chronic musculoskeletal pain still remains unclear, with limited and contrasting evidence in support of their use (Mason et al., 2004; Derry et al., 2014).

Safety and toxicity

Camphor, if accidentally ingested, is a well-recognized toxic compound, and its consumption can result in neurologic symptoms like severe nausea, vomiting, convulsions, lethargy, ataxia, and even death (Manoguerra et al., 2006). A single, even nonlethal, ingested dose of camphor can cause abortion, while a chronic intake has demonstrated hepatotoxic effects (Martin et al., 2004). Camphor is highly toxic if accidentally ingested by infants and small children, being deadly even at a small single dose (Euwema and Swanson, 2019). In a study conducted in Cambodia, where TB® is rubbed on infants for several conditions (varying from rash to the common cold to muscle pains), the use of this product was found to be associated with low levels of thiamine among pediatric patients, although it wasn't clear whether TB®, once absorbed, could directly influence this vitamin metabolism or it was simply a marker of some yet unidentified exposure which can impair thiamine levels (Keating et al., 2015). In another observational study with Cambodian children it was tested the hypothesis that camphor-based topical products like TB® could trigger beriberi-simulating tachypnea, regardless of any influence on thiamine deficiency (Johnson et al., 2017). Nineteen children (9 with tachypnea and 10 healthy subjects) using TB® were analyzed and no camphor was found in their blood, thus possibly indicating that this compound, when applied topically at small doses, is not related with tachypnea in Cambodian infants (Johnson et al., 2017). Howev-

er, case reports of dermal exposure to topical camphor-containing remedies among small children have described possible side effects like severe status epilepticus and impairment of liver function, thus underscoring the potential toxicity of camphor among children even if only applied topically and not ingested (Uc et al., 2000; Guilbert et al., 2007). Moreover, chronic dermal exposure to camphor-based products has been associated with the occurrence of systemic effects, contact dermatitis, and significant allergic responses (Ford, 2001).

Menthol can cause skin allergy and even systemic allergic reactions (Martin et al., 2004). Clove and cinnamon oil can cause allergic contact dermatitis too (Sánchez-Pérez and García-Díez, 1999). An in-vitro study has suggested that clove oil and eugenol may have cytotoxic properties towards human fibroblasts and endothelial cells, thus underscoring the need for further investigation on the topic (Prashar et al., 2006).

Methyl salicylate (contained in formulations like the liquid TB® liniment, but not in Red or White TB® ointments) can be toxic if accidentally ingested and it is documented that, in children less than six years of age, a teaspoon or less of wintergreen oil (containing 98% of methyl salicylate) has been implicated in several deaths (Davis, 2007). Studies have demonstrated that, when topically applied, local tissue levels of salicylate from methyl salicylate formulations should be approximately 30-fold higher than plasma concentrations (Cross et al., 1998). However, in a review of the scientific literature, seventeen cases of salicylism following the topical application of salicylate preparations both in pediatric and in adult patients with dermatologic diseases (mostly psoriasis or ichthyosis) have been reported (Brubacher and Hoffman, 1996). Topical analgesic preparations with methyl salicylate may cause irritant or allergic contact dermatitis, as well as anaphylactic reactions (Chan, 1996), and their excessive usage in patients under treatment with warfarin may result in adverse interactions and bleedings (Chan, 1996; Joss and LeBlond, 2000). A study reported the case of a patient applying over skin a topical remedy containing menthol and methyl salicylate followed by the use of a heating pad, who experienced skin and muscle necrosis as well as persistent interstitial nephritis (Heng, 1987).

In a study involving 24 healthy subjects, the dermal absorption of camphor, menthol, and methyl salicylate contained in medicated patches has been investigated (Martin et al., 2004). Each patch had 46.80 mg of camphor, 37.44 mg of menthol, and 74.88 mg of methyl salicylate (Martin et al., 2004). When two patches were applied, low plasma concentrations of these compounds were measured, near the limits of quantitation for each substance (Martin et al., 2004). Average C_{max} values and standard deviation for camphor, menthol, and methyl salicylate were, respectively, 13.5 ± 4.8 ng/mL, 7.6 ± 2.6 ng/mL, and 8.6 ± 3.8 ng/mL, and these compounds were not detectable beyond 8 to 12 hours after application (Martin et al., 2004). The authors concluded that, for the number of tested patches (up to 8 at a single time), there should be a relatively low systemic exposure to these potentially toxic compounds (Martin et al., 2004).

The U.S. department of Health & Human Services reports that TB® ointments are only for external use (due to its toxicity if accidentally ingested), and any contact with eyes, genital area or damaged skin should be avoided (Household Products Database, 2019). It is also recommended not to use them for more than 7 days, especially if symptoms persist or worsen, and not to apply any tight bandage over treated area (Household Products Database, 2019). Possible side effects may be allergic reactions or severe irritation (Lee and Lam, 1990; Leow et al., 1995; Leow, 1997; Lim et al., 2007; Schliemann et al., 2011; Shih et al., 2015; Anggraini et al., 2017). Moreover, considering available evidence on topical products with camphor, TB® ointments shouldn't be used in children, as well as in pregnant or lactating women. Formulations with methyl salicylate shouldn't be recommended for patients taking anticoagulants or antiplatelet agents. The use of TB® ointments should never be followed by the application of heating pads. Patients with history of contact allergy should be patch tested with the product before applying it over a large body surface, since, as reported by our meta-analysis of prevalence, it might be estimated that around 4% of such pa-

tients could be allergic to TB® ointments too (Fig. 2).

CONCLUSIONS

Based on available evidence, TB® ointments might be useful for the management of pain due to muscular tension and seem capable of increasing skin and muscle blood flow, especially if coupled with massage. However, the most relevant findings of this review regard safety and tolerability of TB® ointments. Among possible adverse events following application of TB® ointments, the most reported ones seem contact skin irritation and allergic reactions. Moreover, considering available evidence on topical products with camphor, TB® ointments shouldn't be used in children, as well as in pregnant or lactating women. Formulations with methyl salicylate shouldn't be recommended for patients taking anticoagulants or antiplatelet agents. Chronic use, large amounts of balm, and the application on damaged skin must be avoided too. Caution is recommended in the use of TB® ointments among patients with any history of contact skin allergy. Further studies are recommended to thoroughly outline the safety and tolerability profile of TB® ointments, as well as to better understand their efficacy in the symptomatic management of painful muscle problems.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTION:

Contribution	Antonelli M	Donelli D	Valussi M
Concepts or ideas	x	x	x
Design	x	x	
Definition of intellectual content	x	x	x
Literature search	x	x	
Experimental studies			
Data acquisition	x	x	x
Data analysis	x	x	x
Statistical analysis	x	x	
Manuscript preparation	x	x	x
Manuscript editing	x	x	x
Manuscript review	x	x	x

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