An Acad Bras Cienc (2023) 95(3): e20200447 DOI 10.1590/0001-3765202320200447
Anais da Academia Brasileira de Ciências | *Annals of the Brazilian Academy of Sciences*
Printed ISSN 0001-3765 I Online ISSN 1678-2690
www.scielo.br/aabc | www.fb.com/aabcjournal

HEALTH SCIENCES

In vivo efficacy of turmeric (*Curcuma longa* L.) in the treatment of peripheral neuropathy: A systematic review of animal models

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Abstract: We report on a systematic review of the efficacy of turmeric derivatives for the *in vivo* treatment of peripheral neuropathies. Our review protocol followed the PRISMA Statement. The Medline (PubMed), Web of Science, Scopus, and Scielo databases were used. The search strategy was ("neuropathy" OR "neuropathies" OR "nerve injury" OR "nerve injuries") AND ("curcumin" OR "turmeric yellow" OR "yellow, turmeric" OR "diferuloylmethane"). Eligibility criteria were *in vivo* animal models, published in English, Portuguese, Spanish, or French, evaluating the efficacy of turmeric derivatives in the treatment of peripheral neuropathies. We have included 30 papers, and all consisted of pre-clinical trials with good methodological quality. Animals treated with turmeric derivatives (i.e., curcumin, curcumin by-products and curcumin loaded delivery systems) demonstrated remarkable amelioration in the injuries caused by diabetic and sciatic neuropathy, as well as for vincristine, cisplatin, and alcohol-induced neuropathy, especially with regards to the functional recovery of the affected nerve. Turmeric has great potential for the treatment of peripheral neuropathies, including those associated with diabetes mellitus. Clinical trials still need to be performed to assess the feasibility of human treatment as an alternative or adjuvant to existing pharmacological therapy.

Key words: Alcoholic neuropathy, diabetic neuropathies, peripheral nervous system diseases, sciatic neuropathy, turmeric.

INTRODUCTION

Neuropathies are common illness related to many systemic or peripheral nervous system (PNS) disorders (Félix & Oliveira 2018). The estimated prevalence of peripheral neuropathies (PN) is about 2% in the population worldwide and in adults over 55 years can reach 8% (Kraychete & Sakata 2011). Furthermore, PN affect around 50% of patients with diabetes mellitus, so that the diabetic peripheral neuropathy (DPN) influences either their physical health, and ability to be physically active, thus remarkably impairing quality of life (Oliveira & Júnior 2018).

There is no pharmacological treatment that avoids or reverses PN, so the treatment often aims at reducing the risk of developing neuropathy, preventing its secondary complications, and relieving painful symptoms (Fernandes et al. 2001). Notwithstanding, majority of the used drugs have several adverse effects that restrict their full clinical exploration (Greeshma et al. 2015).

In the seek for safer and more affective therapeutic options for the amelioration of PN, the focus of scientific investigations has been shifting towards the herbal products (Forouzanfar & Hosseinzadeh 2018). Curcumin (1,7-bis (4-hidroxy-3-methoxiphenyl)

-1,6- heptadiene-3,5-dione) is a phytochemical from dried and powdered rhizomes of *Curcuma longa* L. (Zingiberaceae), a food-flavoring known worldwide as turmeric (Filho et al. 2000, Ma et al. 2013, Brasil 2015, Hewlings & Kalman 2017), that has demonstrated efficacy in the treatment of hyperalgesia (i.e., slow conduction of large fibers) (Daugherty et al. 2018). Curcumin and its derivatives are acknowledged for their powerful anti-inflammatory, antioxidant, and neuroprotective properties, together with the advantages of low toxicity and high dose tolerability in humans (Agthong et al. 2015), thus emerging as a promising strategy for treating DPN and other PN (Hewlings & Kalman 2017, Daugherty et al. 2018).

Indeed, it has been described that curcumin may promote regeneration and functional recovery of damage in peripheral nerves such as the sciatic nerve and may protect the dorsal root ganglion structure following sciatic nerve injury. Moreover, it can also stimulate proliferation, migration, and differentiation of Schwann cells, which consist of particular PNS glial cells that participate in the entire peripheral nerve regeneration process (Zhao et al. 2017).

Even though such preclinical properties have been demonstrated, there is still divergence between research so far on the efficacy of turmeric for the treatment of PN. From a therapeutic point of view, clarifying these issues by means of high evidence level publications should be of great interest for both the academic community and those dealing with clinical practice in the real world. Henceforth we report on a systematic literature review of the *in vivo* efficacy of turmeric in treating PN in animal models.

MATERIALS AND METHODS

Study design: A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline - The PRISMA Statement (Moher et al. 2009).

Hypothesis: Turmeric derivatives are effective in the *in vivo* treatment of PN in animal models.

Guiding question: Have turmeric derivatives demonstrated efficacy in the *in vivo* treatment of PN in animal models?

Eligibility criteria: From the guiding question the acronym "PICOS" was established: "P" (population): animals with peripheral neuropathy; "I" (intervention): administration of turmeric derivatives; "C" (control): animals with peripheral neuropathy that were not treated with turmeric derivatives; "O" (outcome): results from pain-related behavioral test (mechanical allodynia, thermal hyperalgesia, cold allodynia, etc.), electrophysiological analysis, morphometric parameters and walking track analysis; "S"(study design): *in vivo* preclinical trials. Those articles describing the results of *in vivo* animal models evaluating the effect of turmeric or its derivatives in the treatment of PN were considered eligible. Only articles published in English, Portuguese, French, or Spanish were included. No time limit was imposed for the selection of articles. The *in vitro* studies, clinical trials, reports of the use of turmeric together with another substance, and those that did not use behavioral tests to assess peripheral neuropathy were excluded. Review articles, publications in conference proceedings, editorials, letters to the editor, news items, commentaries, dissertations, and thesis were also excluded.

Information sources: The search was performed in the Medline (PubMed), Web of Science, Scopus, and Scielo databases with studies published up to June 29, 2019. The

starting date of the collection was not restricted, since the aim was to recover the maximum number of articles dealing with the efficacy of turmeric in the *in vivo* treatment (preclinical) of PN, regardless of the year of publication. The authors of the unavailable articles were contacted twice by e-mail, through which access to these articles was requested.

Search strategy: The definition of the descriptors was performed using the Medical Subject Headings (MeSH) and the Health Sciences Descriptors (DeCS). To perform the search, the options "Advanced search" and "All fields" were selected. The keywords were combined with Boolean operators for the search strategy: ("neuropathy" OR "neuropathies" OR "nerve injury" OR "nerve injuries") AND ("curcumin" OR "turmeric yellow" OR "yellow, turmeric" OR "diferuloylmethane").

Selection of **the studies:** Research data were extracted and exported to the Rayyan QCRI platform (Ouzzani et al. 2016) to facilitate the selection of potentially eligible studies. The selection of the studies consisted of two steps and was performed independently by two researchers (RSS and CPD) to bypass bias in the selection and exclusion of the papers: i) after selection of the papers from each database the duplicates were excluded; ii) a preliminary reading of the title and abstract of the articles was subsequently performed. In cases of disagreement between the two researchers, a third researcher evaluated the paper, and by consensus the final decision of the articles to be included herein was taken.

Data collection: The articles that met the inclusion criteria were read in full, and during this phase the variables collected were: authors, year of publication, origin of the publication, type of turmeric derivative, administered dose, type of animal, sample size of intervention and control group, treatment time spam, type of peripheral neuropathy, neuropathy induction methods, neuropathy evaluation methods, and main outcomes (Tables I - III). In addition, a flowchart was constructed summarizing the number of articles included and excluded in each step, according to the established criteria (Fig. 1), as recommended by PRISMA (Moher et al. 2009)

Quality evaluation: The SYRCLE (Hooijmans et al. 2014) tool was used to assess the quality of preclinical trials. Such a tool assesses the risk of bias for animal studies and contains the following assessment categories: selection bias; performance bias; detection bias; friction bias; reporting bias; and other sources of bias. Ten questions were applied to the papers included in the systematic review, whose answers may be "LOW" indicating low risk of bias, "HIGH" indicating high risk of bias, and "UNCERTAIN" indicating uncertain risk. It is not recommended to calculate the sum of each individual study when using this tool (Hooijmans et al. 2014). The evaluation of the methodological quality of the studies included in the systematic review was also independently performed by two researchers (RSS and CPD) and divergences between assessments were resolved by reaching a consensus with a third researcher.

Data analysis: After reading the studies in full, data were extracted from each study and inserted and organized into an electronic spreadsheet. Descriptive statistics were used for data summarization, analysis, and interpretation.

Table I. Type of turmeric derivative, administered dose, type of animal, size of intervention and control groups (n) and treatment duration for the included papers.

Author/Year	Type of turmeric derivative	Administered dosage	Type of animal	n of intervention and control groups	Treatment duration
Ceyhan et al. 2018	curcumin	100 mg/Kg	Sprague-Dawley male rats	CG: 10, IG: 10	14 days
Daugherty et al. 2018	J147 curcumin derivative	10 and 50 mg/Kg	Swiss Webster female mices	CG: 8, IG: 8	20 weeks
Jia et al. 2018	curcumin nanocapsules	4 mg/Kg	Sprague-Dawley male rats	CG: 7, IG: 7	10 weeks
Pierreti et al. 2017	PLGA curcumin nanovesicles	20 and 60 mg/Kg 5 and 25 µg/rat (intratecal)	CD-1 male rats	CG: 12, IG: 12	10 days
Liu et al. 2016a	curcumin	40, 20 and 10 mg/Kg	BALB / c male mices	CG: 10, IG: 10	1, 2, 4, 8 weeks
Liu et al. 2016b	curcumin	30, 60 and 120 mg/Kg	BALB / c male mices	CG: 8, IG: 8	7 days
Ma et al. 2016	curcumin	50, 100, 300 mg/Kg	Sprague-Dawley male rats	CG: 10, IG: 10	4 weeks
Abd Allah & Gomaa 2015	curcumin	100 mg/Kg	Wistar male rats	CG: 6, IG: 6	6 weeks
Adhikari et al. 2015	curcumin	300 mg/Kg	Sprague-Dawley male rats	CG: 6, IG: 6	7 weeks
Agthong et al. 2015	curcumin	200 mg/Kg	Wistar female rats	CG: 8, IG: 8	5 weeks
Babu et al. 2015	curcumin	15, 30 and 60 mg/Kg	Swiss albino male mices	CG: 6, IG: 6	14 days
Greeshma et al. 2015	tetrahydrocurcumin	40 and 80 mg/Kg	Wistar male rats	CG: 6, IG: 6	14 days
Meng et al. 2015	curcumin	100 mg/Kg	Sprague-Dawley male rats	CG: 6, IG: 6	14 days
Yuce et al. 2015	curcumin	100 mg/Kg	Wistar albino female rats	CG: 15, IG: 15	4 weeks
Cao et al. 2014	curcumin	100 mg/Kg	Sprague-Dawley male rats	CG: 6, IG: 6	14 days
Zhao et al. 2014a	curcumin	45 mg/Kg	ICR male rats	CG: 8 to 12, IG: 8 to 12	21 days
Zhu et al. 2014	curcumin	20, 40 and 60 mg/Kg	Sprague-Dawley male rats	CG: 20, IG: 10	14 days
Zanjani et al. 2014	curcumin	1.5; 25 and 50 mg/Kg	Wistar male rats	CG: 8, IG: 8	7 days
Zhao et al. 2014b	curcumin	200 mg/Kg	Sprague-Dawley male rats	CG: 6, IG: 6	14 days
Nagilla et al. 2014	curcumin	50 mg/Kg	Wistar male rats	CG: 10, IG: 10	2 weeks
Banafshe et al. 2014	curcumin	50 mg/Kg	Wistar albino male rats	CG: 10, IG: 10	15 days
Jeon et al. 2013	cucumin	50 mg/Kg	Sprague-Dawley male rats	CG: 10, IG: 10	7 days
Joshi et al. 2013	curcumin and curcumin SNEDDS	30, 100 and 300 mg/Kg	Sprague-Dawley male rats	CG: 6 to 8, IG: 6 to 8	2 weeks
Li et al. 2013	curcumin	60 mg/Kg	Sprague-Dawley male rats	CG: 12, IG: 12	28 days
Ma et al. 2013	curcumin	50, 100, 300 mg/Kg	Sprague-Dawley male rats	CG: 8, IG: 8	4 weeks
Mohammadi et al. 2013	curcumin	10 mL of curcumin (5 mg/mL)	Wistar male rats	CG: 15, IG: 15	12 weeks
Kandhare et al. 2012	curcumin	20, 40 and 80 mg/Kg	Wistar male rats	CG: 6, IG: 6	10 weeks
Patzkó et al. 2012	curcumin	100 mg/Kg	R98C knock-in mices	CG: 5 to 10, IG: 5 to 10	3 meses
Zhao et al. 2012	curcumin	5, 15 and 45 mg/Kg	C57BL/6J male mices	CG: 8 to 12, IG: 8 to 12	3 weeks
Sharma et al. 2007	curcumin	60mg/Kg	Laka line albino male rats	CG: 6 to 7 IG: 6 to 7	4 weeks

CG: control group; IG: intervention group (i.e. with turmeric derivative administered).

Table II. Types of neuropathy, induction and evaluation methods in the included papers.

Author/Year	Types of neuropathy	Induction methods	Evaluation methods
Ceyhan et al. 2018	SN	Chronic sciatic nerve constriction injury	PT, VFFS, CPT
Daugherty et al. 2018	DN	DM induced by intraperitoneal injection of streptozotocin (90 mg/Kg)	HPT, MNCV, VFFS
Jia et al. 2018	DN	DM induced by intraperitoneal injection of streptozotocin (30 mg/Kg)	VFFS and PT
Pierreti et al. 2017	SN	Chronic sciatic nerve constriction injury	FT, PT + zymosan, VFFS
Liu et al. 2016a	SN	Sciatic nerve amputation	MNCV
Liu et al. 2016b	SN	Chronic sciatic nerve constriction injury	VFFS, CAT (acetone)
Ma et al. 2016	DN and SN	DM induced by intraperitoneal injection of streptozotocin (50 mg/Kg) and Chronic sciatic nerve constriction injury	HPT, VFFS, MNCV, S
Abd Allah & GOMAA 2015	DN	DM induced by intraperitoneal injection of streptozotocin (100 mg/Kg)	VFFS, HPT, TFT
Adhikari et al. 2015	DN	DM induction by high-fat diet for 2 weeks with or without intraperitoneal injection of streptozotocin (35 mg/Kg)	HPT, TFT
Agthong et al. 2015	cisplatin-induced neuropathy	Intraperitoneal injection of cisplatin (2 mg/Kg), twice/week for 5 weeks	HPT, MNCV
Babu et al. 2015	vincristine-induced neuropathy	Intraperitoneal injection of vincristine sulphate (0.1 mg/Kg/day) for 7 days	HPT, CPT, TBT, RRT, SFI, FT
Greeshma et al. 2015	vincristine-induced neuropathy	Intraperitoneal injection of vincristine sulphate (75 mg/Kg) for 10 days	HPT, CPT, RST, SFI, RRT, FT
Meng et al. 2015	DN	DM induction by high-fat and high-fructose diet for 8 weeks	PT, TBT
Yuce et al. 2015	SN	Chronic sciatic nerve constriction injury	SFI
Cao et al. 2014	SN	Chronic sciatic nerve constriction injury	PT, VFFS
Zhao et al. 2014a	SN	Chronic sciatic nerve constriction injury	RRT, locomotor activity, PT
Zhu et al. 2014	SN	Chronic sciatic nerve constriction injury	VFFS, PT
Zanjani et al. 2014	SN	Chronic sciatic nerve constriction injury	VFFS, CAT (acetone)
Zhao et al. 2014b	DN	DM induced by intraperitoneal injection of streptozotocin (60 mg/Kg)	VFFS
Nagilla et al. 2014	DN	DM induced by intraperitoneal injection of streptozotocin (60 mg/Kg)	HPT, VFFS
Banafshe et al. 2014	DN	DM induced by intraperitoneal injection of streptozotocin (60 mg/Kg)	PT, VFFS
Jeon et al. 2013	SN	Chronic sciatic nerve constriction injury	VFFS
Joshi et al. 2013	DN	DM induced by intraperitoneal injection of streptozotocin (55 mg/Kg)	VFFS, TFT, RST, MNCV
Li et al. 2013	DN	DM induced by intraperitoneal injection of streptozotocin (65 mg/Kg)	VFFS, PT
Ma et al. 2013	SN	Chronic sciatic nerve constriction injury	HPT, VFFS, MNCV
Mohammadi et al. 2013	SN	Chronic sciatic nerve constriction injury	SNFR, SFI, SNSI
Kandhare et al. 2012	Alcoholic neuropathy	ethanol (35% v/v), 10 g/Kg	RST, VFFS, TFT, MNCV
Patzkó et al. 2012	type 1B Charcot–Marie–Tooth disease	R98C gene mutation	RRT
Zhao et al. 2012	SN	Chronic sciatic nerve constriction injury	VFFS, HPT
Sharma et al. 2007	DN	DM induced by intraperitoneal injection of streptozotocin (200 mg/Kg)	TFT, HPT

CAT: cold allodynia test; CPT: cold plate test; DM: Diabetes mellitus; DN: diabetic neuropathy; FT: formalin test; HPT: hot plate test; MNCV: motor nerve conduction velocity; PT: plantar test; RRT: rota-rod test; RST: Randall Sellito test; SFI: sciatic functional index, SN: sciatic neuropathy; SNFR: sciatic nerve functional recovery; SNSI: sciatic nerve static index; TBT: tick bite test; TFT: tail flick test; VFFS: Von Frey filament stimulation.

Table III. Main outcomes of the included papers.

Author/Year	Main outcomes
Ceyhan et al. 2018	There was no significant difference between IG and CG for PT, VFFS and CPT.
Daugherty et al. 2018	GI presented increased hind paw withdrawal latency for HPT ($p < 0.0001$) and increased tactile withdrawal threshold for VFFS compared to CG ($p < 0.0001$) (rat with neuropathy had mechanical hyperalgesia and no change was observed regarding thermal sensitivity). There was no significant difference between IG and CG for MNCV.
Jia et al. 2018	GI showcased increased hindpaw withdrawal latency for PT ($p < 0.01$) and increased tactile withdrawal threshold for VFFS compared to CG ($p < 0.01$) (rat with neuropathy had both mechanical and thermal hyperalgesia).
Pierreti et al. 2017	IG showed a decrease in paw withdrawal time in FT ($p < 0.01$), decreased tactile withdrawal threshold for VFFS ($p < 0.01$) and decreased hind paw withdrawal latency in PT + zymosan ($p < 0.05$) (thermal and mechanical sensitivity between rats with neuropathy and rats without neuropathy were not compared).
Liu et al. 2016a	IG showed an increase in MNCV ($p < 0.05$) compared to CG.
Liu et al. 2016b	IG showed decreased paw withdrawal latency in CAT ($p < 0.01$) and increased tactile withdrawal threshold for VFFS compared to CG ($p < 0.01$) (rat with neuropathy had mechanical hyperalgesia and thermal hypoalgesia).
Ma et al. 2016	IG presented decreased hind paw withdrawal latency for HPT ($p < 0.05$) and decreased tactile withdrawal threshold for VFFS compared with CG ($p < 0.05$) and increased MNCV ($p < 0.05$) and increased SFI ($p < 0.05$) (rat with neuropathy had mechanical and thermal hypoalgesia).
Abd Allah & Gomaa 2015	IG had increased reaction time for HPT ($p < 0.05$), increased latency response for TFT ($p < 0.05$), increased tactile withdrawal threshold for VFFS ($p < 0.05$) compared with CG (mouse with neuropathy had hyperalgesia thermal).
Adhikari et al. 2015	IG showed increased reaction time for HPT ($p < 0.001$) and increased latency response for TFT ($p < 0.001$) compared to CG (rat with neuropathy had thermal hyperalgesia).
Agthong et al. 2015	IG showed decreased reaction time for HPT ($p < 0.05$) and increased MNCV ($p < 0.05$) compared CG (rat with neuropathy had thermal hypoalgesia).
Babu et al. 2015	IG showed increased reaction time for HPT ($p < 0.001$) and CPT ($p < 0.001$), decreased tail peeling time in TBT ($p < 0.001$), decreased paw lift time ($p < 0.001$) and paw licking ($p < 0.01$) in the FT, and increase in SFI ($p < 0.001$) compared to CG. There was no significant difference between GI and CG in the RRT (rat with neuropathy had thermal hyperalgesia and mechanical hypoalgesia).
Greeshma et al. 2015	IG presented increased tactile withdrawal latency for HPT ($p < 0.001$) and CPT ($p < 0.001$), increased mechanical threshold for RST ($p < 0.001$), increased SFI ($p < 0.001$) and decreased paw elevation time ($p < 0.001$) and paw licking ($p < 0.01$) in the FT compared to CG (rat with neuropathy had thermal and mechanical hyperalgesia). There was no significant difference between the groups in the RRT.
Meng et al. 2015	IG presented increased hind paw withdrawal latency for PT ($p < 0.05$) and increased tactile withdrawal threshold in the TBT compared to CG ($p < 0.05$) (rat with neuropathy had mechanical and thermal hyperalgesia).
Yuce et al. 2015	IG presented increase of SFI ($p < 0.05$) compared to CG.
Cao et al. 2014	IG presented increased hind paw withdrawal latency for PT ($p < 0.05$) and increased tactile withdrawal threshold for VFFS compared to CG ($p < 0.05$) (rat with neuropathy had thermal and mechanical hyperalgesia).
Zhao et al. 2014a	IG presented increased hind paw withdrawal latency for PT ($p < 0.01$) compared to CG (rat with neuropathy had thermal hyperalgesia). There was no significant difference between IG and CG in the RRT and the locomotor activity test.
Zhu et al. 2014	IG presented increased hind paw withdrawal latency for PT ($p < 0.05$) and VFFS ($p < 0.05$) compared to CG (rat with neuropathy had thermal and mechanical hyperalgesia).
Zanjani et al. 2014	IG presented increased paw withdrawal latency for VFFS ($p < 0.001$) and decreased paw withdrawal frequency in the CAT ($p < 0.001$) (rat with neuropathy had mechanical and thermal hyperalgesia compared to rat without neuropathy).

Table III. Continuation.

Zhao et al. 2014b	IG presented increased paw withdrawal latency for VFFS (p <0.05) compared to CG (rat with neuropathy had mechanical hyperalgesia).
Nagilla et al. 2014	IG presented decreased hindpaw withdrawal latency for HPT (p <0.05) and increased tactile withdrawal threshold for VFFS (p <0.001) compared to CG (rat with neuropathy had mechanical hyperalgesia and thermal hypoalgesia).
Banafshe et al. 2014	IG presented lowering in hind paw withdrawal latency for PT (p <0.05) and increased tactile withdrawal threshold for VFFS compared to CG (rat with neuropathy had thermal hypoalgesia and mechanical hyperalgesia).
Jeon et al. 2013	IG presented increased tactile withdrawal threshold for VFFS compared to CG (p <0.05) (rat with neuropathy had mechanical hyperalgesia).
Joshi et al. 2013	IG presented increased tail withdrawal latency for TFT (hot) (p <0.01) and TFT (cold) (p <0.01) and increased tactile withdrawal threshold for VFFS (p <0.01) and RST (p <0.01) and increased MNCV (p <0.01) compared to CG (rat with neuropathy had mechanical and thermal hyperalgesia).
Li et al. 2013	IG presented increased hindpaw withdrawal latency for PT (p <0.04) and increased tactile withdrawal threshold for VFFS compared to CG (p <0.03) (rat with neuropathy had mechanical and thermal hyperalgesia).
Ma et al. 2013	IG presented decreased hindpaw withdrawal latency for HPT (p <0.01), decreased tactile withdrawal threshold for VFFS (p <0.01), increased MNCV (p <0.01) and increased SFI (p <0.01) compared with CG (rat with neuropathy had mechanical and thermal hypoalgesia).
Mohammadi et al. 2013	IG presented greater SNFR (p <0.05), increase in SFI (p <0.05) and SNSI (p <0.05) compared to CG.
Kandhare et al. 2012	IG showed increased tail-lift latency for TFT (p <0.001), increased tactile withdrawal threshold for VFFS (p <0.001) and RST (p <0.001) and increased MNCV (p <0.001) compared with CG (rat with neuropathy had mechanical and thermal hyperalgesia).
Patzkó et al. 2012	There was no significant difference between IG and CG in the rota-rod test.
Zhao et al. 2012	IG presented increased paw withdrawal latency for VFFS (p <0.01) and increased hind paw withdrawal latency for HPT (p <0.01) compared to CG (rat with neuropathy had mechanical and thermal hyperalgesia).
Sharma et al. 2007	IG presented increased hind paw withdrawal latency for HPT (p <0.05) and increased latency response for TFT (p <0.05) (rat with neuropathy had thermal hyperalgesia).

CG: control group; CAT: cold allodynia test; CPT: cold plate test; DM: Diabetes mellitus; DN: diabetic neuropathy; FT: formalin test; HPT: hot plate test; IG: intervention group (i.e. with turmeric derivative administered); MNCV: motor nerve conduction velocity; PT: plantar test; RRT: rota-rod test; RST: Randall Sellito mechanical hyperalgesia test; SFI: sciatic functional index; SN: sciatic neuropathy; SNFR: sciatic nerve functional recovery; SNSI: sciatic nerve static index; TBT: tick bite test; TFT: tail flick test; VFFS: Von Frey filament stimulation**.**

RESULTS

General features of the included studies

Figure 1 summarizes the flow of information through the different phases of this systematic review. A total of 399 articles were found in the selected databases, using the MeSH and DeCS descriptors, of which 235 were found in Scopus, 99 in Web of Science, 65 in PubMed, with no articles being found in the Scielo database. No articles were included from other sources/ gray literature. From the total, 99 articles were excluded due to duplication.

In the first screening, in which the title and summary of each article were analyzed, 261 studies were excluded. The reasons for their exclusions were: being not original articles (n = 160); did not evaluate the use of turmeric in PN (n = 66); being *in vitro* studies (n = 18); were not in the selected languages (n = 12); evaluated the use of turmeric together with another substance (n = 2); being unavailable (n = 2); and evaluated the use of turmeric in cells taken from mice (n = 1). In the second screening, after reading all the full articles, nine studies were excluded

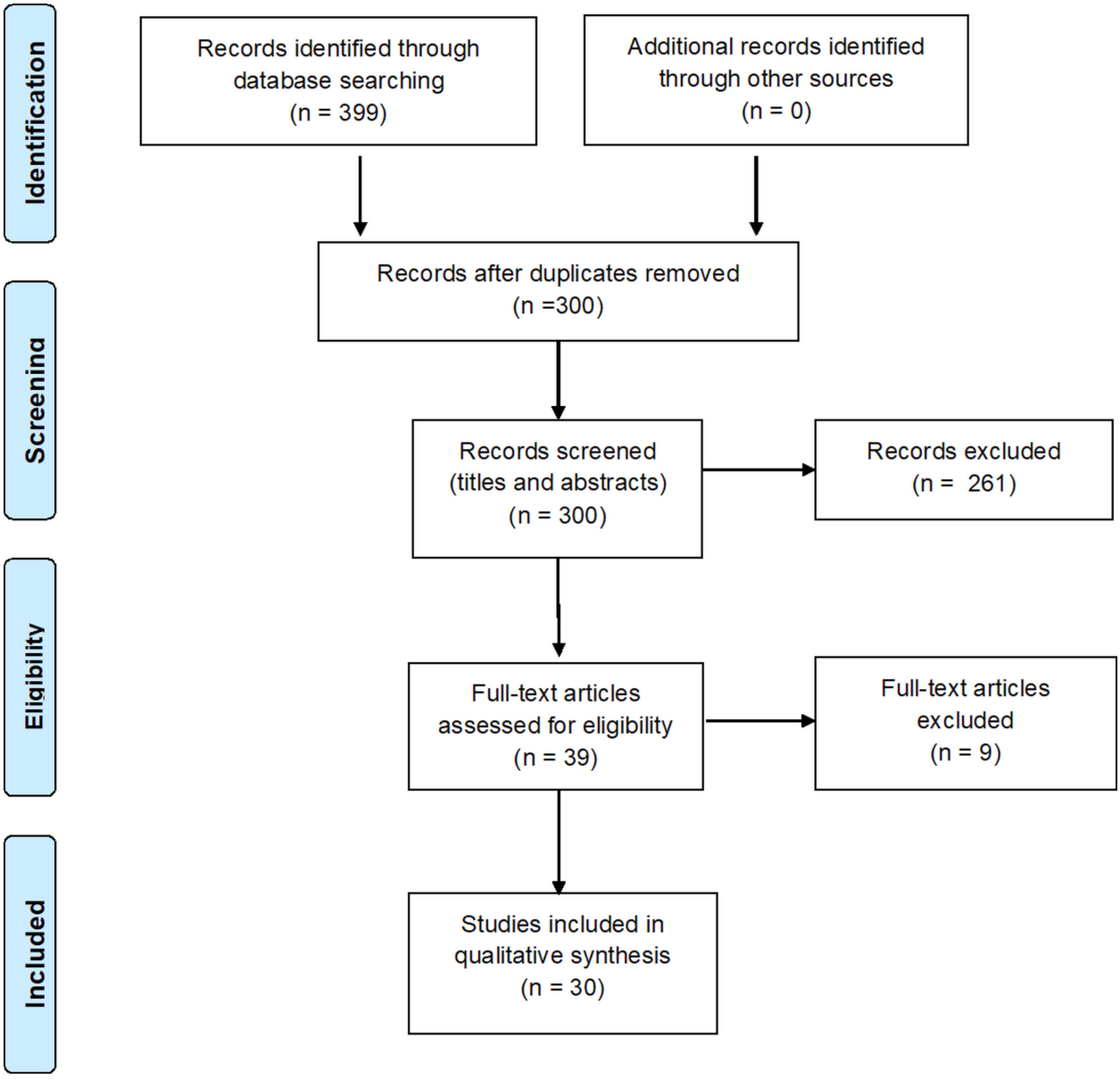

Figure 1. PRISMA flowchart specifying the search for articles in the systematic review of the efficacy of turmeric in the treatment of peripheral neuropathy. From: [15]. Preferred Reporting Items for Systematic Reviews and Meta-analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org[15].

because they did not use behavioral tests to assess neuropathy (n = 4); were unavailable (n = 3); and evaluated the use of turmeric in cells taken from mice (n = 2). Full analysis of these articles revealed that 30 studies fulfilled the inclusion criteria (Fig. 1), all in the English language. Articles that were unavailable during the screening, even with twice contacting the author directly, could not be obtained.

Figures 2a and 2b and Table I show the characteristics of the selected studies. Publications between 2007 and 2018 were found (Figure 2a), most of them (63 %) having been published in 2013 (n = 6), 2014 (n = 6) and 2015 (n = 7). Concerning the origin of these publications,

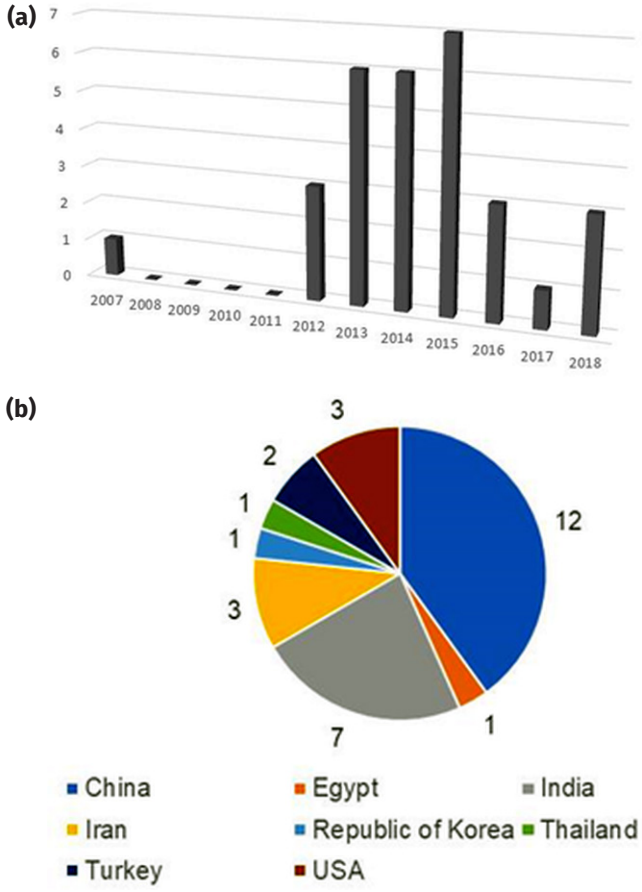

Figure 2. Overview of year of publication (a) and origin (b) of the manuscripts included in the systematic review of the efficacy of turmeric in the treatment of peripheral neuropathy (n = 30).

90 % (n = 27) of the papers were from Asian countries.

Types and doses of turmeric derivatives

The turmeric derivatives were used in oral doses ranging from 4 mg/Kg up to 300 mg/Kg. Twenty-five studies (Sharma et al. 2007, Khandare et al. 2012, Patzkó et al. 2012, Zhao et al. 2012, Banafshe et al. 2014, Jeon et al. 2013, Li et al. 2013, Ma et al. 2013, Mohammadi & Mahmoodi 2013, Cao et al. 2014, Nagilla & Reddy 2014, Zanjani et al. 2014, Zhao et al. 2014a, Zhao et al. 2014b, Zhu et al. 2014, Abd Allah & Gomaa 2015, Adhikari et al. 2015, Agthong et al. 2015, Babu et al. 2015, Meng et al. 2015, Yuce et al. 2015, Liu et al. 2016a, 2016b, Ma et al. 2016, Ceyhan et al. 2018) (83.3 %) used pure curcumin; one (Pieretti et al. 2017) (3.3 %) used curcumin containing poly(lactic-co-glycolic acid) (PLGA) nanovesicles; one (Joshi et al. 2013) (3.3 %) used the curcumin Self Nanoemulsifying Drug Delivery System (SNEDDS); one (Jia et al. 2018) (3.3 %) used nanoencapsulated curcumin, one (Greeshma et al. 2015) (3.3 %) used the curcumin derivative tetrahydrocurcumin; and one (Daugherty et al. 2018) (3.3 %) the J147 curcumin derivative.

Animal strains

Several animal models were used for assessing the effects of turmeric in the PN. Eleven studies (Zhao et al. 2011, Jeon et al. 2013, Joshi et al. 2013, Li et al. 2013, Cao et al. 2014, Zhu et al. 2014, Adhikari et al. 2015, Ma et al. 2015, Meng et al. 2015, Ceyhan et al. 2018, Jia et al. 2018) (40 %) used Sprague-Dawley male rats; seven (Khandare et al. 2012, Banafshe et al. 2014, Mohammadi & Mahmoodi 2013, Nagilla & Reddy 2014, Zanjani et al. 2014, Abd Allah & Gomaa 2015, Greeshma et al. 2015) (23.3 %) used Wistar male rats; two (Agthong et al. 2015, Meng et al. 2015) (7 %) used Wistar female rats; two (Liu et al. 2016a, 2016b) (7 %) used Balb/C male mice; one (Daugherty et al. 2018) (3.3 %) used Swiss female mice; one (Pieretti et al. 2017) (3.3 %) used CD1 mate rats; one (Babu et al. 2014) (3.3 %) used Swiss male mice; and one (Zhao et al. 2014) (3.3 %) used ICR male rats.

Neuropathy induction models and follow up

Table II summarizes the type of neuropathy, induction methods and treatment timeframes of the included papers. Fourteen (Zhao et al. 2011, Jeon et al. 2013, Ma et al. 2013, Mohammadi & Mahmoodi 2013, Cao et al. 2014, Zanjani et al. 2014, Zhao et al. 2014, Zhu et al. 2014, Yuce et al. 2015, Liu et al. 2016a, 2016b, Ma et al. 2016, Pieretti et al. 2017, Ceyhan et al. 2018) (47 %) evaluated sciatic neuropathy; twelve (Sharma

et al. 2007, Joshi et al. 2013, Li et al. 2013, Ma et al. 2013, Zhao et al. 2013, Nagilla et al. 2014, Abd Allah & Gomaa 2015, Adhikari et al. 2015, Meng et al. 2015, Daugherty et al. 2018, Jia et al. 2018, Banafshe et al. 2014) (40 %) diabetic neuropathy; two (Babu et al. 2014, Greeshma et al. 2015) (7 %) vincristine-induced neuropathy; one (Agthong et al. 2015) (3,.3 %) cisplatin-induced neuropathy; one (Khandare et al. 2012) (3.3 %) alcoholic neuropathy and one (Patzkó et al. 2012) (3.3 %) type 1B Charcot-Marie-Tooth disease.

Several methods were used to induce peripheral neuropathy in animals i.e., twelve (Jeon et al. 2013, Zhao et al. 2012, Cao et al. 2014, Zanjani et al. 2014, Zhao et al. 2014, Zhu et al. 2014, Ma et al. 2015, Yuce et al. 2015, Liu et al. 2016a, 2016b, Jia et al. 2018, Ceyhan et al. 2018) (43.3 %) studies performed chronic sciatic nerve constriction injury; eleven (Sharma et al. 2007, Joshi et al. 2013, Li et al. 2013, Zhao et al. 2013, Nagilla et al. 2014, Abd Allah & Gomaa 2015, Adhikari et al. 2015, Meng et al. 2015, Daugherty et al. 2018, Jia et al. 2018, Banafshe et al. 2014) (37 %) administered intraperitoneal streptozotocin injections at doses ranging from 30 mg/Kg to 200 mg/Kg for induction of DPN; two (Babu et al. 2014, Greeshma et al. 2015) (7 %) administered intraperitoneal injections of vincristine sulfate 0.1 mg/Kg/day and 75 mg/Kg, respectively; one (Ising et al. 2018) (3.3 %) used a high-fat diet with or without intraperitoneal injection of streptozotocin 35 mg/Kg to induce DPN; one (Liu et al. 2016a) (3.3 %) performed sciatic nerve amputation; one (Agthong et al. 2015) (3.3 %) administered intraperitoneal injection of cisplatin 2 mg/Kg; one (Khandare et al. 2012) (3.3 %) administered ethanol (35 % v/v) at 10 g/Kg; and one (Patzkó et al. 2012) (3.3 %) performed a mutation in the R98C gene to induce type 1B Charcot-Marie-Tooth disease.

Behavioral tests

The Table II displays the various behavioral tests that were used to evaluate PN. Among the twenty-six studies that evaluated thermal hyperalgesia or hypoalgesia, twelve (Sharma et al. 2007, Zhao et al. 2011, Ma et al. 2013, Babu et al. 2015, Nagilla et al. 2014, Abd Allah & Gomaa 2015, Adhikari et al. 2015, Agtong et al. 2015, Greeshma et al. 2015, Ma et al. 2015, Liu et al. 2016b, Daugherty et al. 2018) (40 %) used the hot plate test (HPT); nine (Daugherty et. al. 2018, Li et al. 2013, Cao et al. 2014, Zhao et al. 2014, Zhu et al. 2014, Meng et al. 2015, Daugherty et al. 2018, Ceyhan et al. 2018, Banafshe et al. 2014) (27 %) the plantar test (PT); three (Babu et al. 2015, Greeshma et al. 2015, Ceyhan et al. 2018) (10%) applied the cold plate test (CPT); two (Zanjani et al. 2014, Liu et al. 2016b) (7 %) the cold allodynia test (CAT); and one (Pieretti et al. 2017) (3.3 %) associated the PT with zymosan.

Of the 24 studies evaluating mechanical hyperalgesia or hypoalgesia, eighteen (Kandhare et al. 2012, Zhao et al. 2012, Jeon et al. 2013, Joshi et al. 2013, Li et al. 2013, Ma et al. 2013, Cao et al. 2014, Nagilla et al. 2014, Zanjani et al. 2014, Zhao et al. 2014, Zhu et al. 2014, Abd Allah & Gomaa 2015, Ma et al. 2016, Liu et al 2016b, Daugherty et al. 2018, Pieretti et al. 2017, Ceyhan et al. 2018, Jia et al. 2018) (60 %) used the Von Frey filament stimulation (VFFS); five (Sharma et al. 2007, Kandhare et al. 2012, Joshi et al. 2013, Abd Allah & Gomaa 2015, Adhikari et al. 2015) (17 %) used the tail flick test (TFT); three (Kandhare et al. 2012, Joshi et al. 2013, Greeshma et al. 2015) (10 %) employed the Randall Sellito test (RST); three (Babu et al. 2015, Greeshma et al. 2015, Pieretti et al. 2017) (10 %) the formalin test (FT), three (Patzkó et al. 2012, Zhao et al. 2014, Greeshma et al. 2015) (10 %) the Rota-Rod test (RRT); and two (Agthong et al. 2015, Meng et al. 2015) (7 %) the tick bite test (TBT).

Seven studies (Kandhare et al. 2012, Joshi et al. 2013, Ma et al. 2013, Agthong et al. 2015, Liu et al. 2016, Ma et al. 2016, Daugherty et al. 2018) (23.3 %) also evaluated motor nerve conduction velocity (MNCV); six (Joshi et al. 2013, Li et al. 2013, Abd Allah & Gomaa 2015, Babu et al. 2015, Ma et al. 2016, Jia et al. 2018) (13.3 %) the sciatic functional index (SFI); one (Zanjani et al. 2014) (3.3 %) assessed locomotor activity; one (Mohammadi & Mahmoodi 2013) (3.3 %) performed the sciatic nerve functional recovery (SNFR) test; and one (Mohammadi & Mahmoodi 2013) (3.3 %) calculated the sciatic nerve static index (SNSI).

Main outcomes

A summary of the main reported outcomes for each included paper is presented in Table III. Herein, to facilitate the comprehension of the gathered evidence, the results were separated in three groups according to the type of neuropathy, namely i) DPN, ii) sciatic neuropathy, and iii) other neuropathies.

Diabetic peripheral neuropathy (DPN)

Among the thirteen studies that evaluated DPN, ten (Sharma et al. 2007, Joshi et al.2013, Li et al. 2013, Ma et al. 2013, Banafshe et al. 2014, Nagilla et al. 2014, Abd Allah & Gomaa 2015, Adhikari et al. 2015, Meng et al. 2015, Ceyhan et al. 2018) (83.3 %) demonstrated improvement in the intervention group as compared to the control group in hyperalgesia or thermal hypoalgesia; ten (Zhao et al. 2012, Banafshe et al. 2014, Joshi et al. 2013, Ma et al. 2013, Mohammadi & Mahmoodi 2013, Nagilla et al. 2014, Zhao et al. 2014, Abd Allah & Gomaa 2015, Daugherty et al. 2018, Jia et al. 2018) (83.3 %) found amelioration in the intervention group as compared to the control group in hyperalgesia or mechanical hypoalgesia; two (Joshi et al. 2013, Ma et al. 2013) (16.6 %) found improvement in the intervention group compared with the control group for MNCV; one study (Ma et al. 2013) (8.3 %) demonstrated improvement for SFI; whereas only one study (Daugherty et al. 2018) (8.3 %) found no significant difference for MNCV.

Sciatic neuropathy

Among the fourteen studies that evaluated sciatic neuropathy, nine (Zhao et al. 2012, Jeon et al. 2013, Ma et al. 2013, Cao et al. 2014, Zanjani et al. 2014, Zhu et al. 2014, Liu et al. 2016b, Ma et al. 2016, Pierreti et al. 2017) (64.3 %) found improvement in the intervention group compared with the control group in hyperalgesia or thermal hypoalgesia, whereas one (Ceyhan et al. 2018) (7.14 %) found no significant difference between the groups; eight (Zhao et al. 2012, Jeon et al. 2013, Ma et al. 2013, Cao et al. 2014, Zhao et al. 2014, Zhu et al. 2014, Liu et al. 2016b, Ma et al. 2016) (57.14 %) verified improvement in the intervention group as compared to the control group in hyperalgesia or mechanical hypoalgesia, whereas one (Ceyhan et al. 2018) (8.3 %) found no significant difference between the groups; three (Ma et al. 2013, Liu et al. 2016a, Ma et al. 2016) (25 %) found improvement in the intervention group compared with the control group for MNCV; four (Ma et al. 2013, Mohammadi & Mahmoodi 2013, Yuce et al. 2015, Ma et al. 2016) (33.3 %) for the SFI; one (Mohammadi & Mahmoodi 2013) (8.3 %) for the SNSI; one (Mohammadi & Mahmoodi 2013) (8.3 %) for functional recovery of the sciatic nerve and one (Zhao et al. 2014) (8.3 %) in the locomotor activity test.

Other neuropathies

Among the three studies (Agthong et al. 2015, Babu et al. 2015, Greeshma et al. 2015) which evaluated vincristine or cisplatin-induced neuropathy, all found improvement in the intervention group compared to the control group in hyperalgesia or thermal hypoalgesia;

two (Babu et al. 2015, Greeshma et al. 2015) (67 %) reported amelioration in the intervention group compared to the control group in hyperalgesia or mechanical hypoalgesia; and one (Agthong et al. 2015) (20 %) found improvement in the intervention group compared with the control group concerning MNCV.

Regarding the only studies that evaluated alcoholic neuropathy (Kandhare et al. 2012) and type 1B Charcot-Marie-Tooth disease (Patzkó et al. 2012), amelioration was observed in the alcoholic neuropathy group compared to the control group in thermal hyperalgesia or hypoalgesia, mechanical hyperalgesia or hypoalgesia, and MNCV. However, no significant difference was found between the type 1B Charcot-Marie-Tooth disease group and the control group for the RRT.

Quality assessment and risk of bias

Table IV presents the results for the methodological quality of the articles as assessed using the SYRCLE scale. Only one study (Banafshe et al. 2014) presented high risk of friction bias, but low risk or uncertain risk for the other biases analyzed. All other articles presented low risk or uncertain risk for all biases analyzed. Therefore, all articles included in this systematic review presented good methodological quality.

DISCUSSION

Most preclinical studies evaluated in this systematic review showed that turmeric had a beneficial effect on the treatment of PN in animal models. All studies included in this systematic review evaluating DPN found that turmeric improved tactile sensitivity to painful stimuli of mechanical and thermal action, which indicates improved conduction of stimuli by the affected nerve. In two (Joshi et al. 2013, Ma et al. 2013) of the three studies that evaluated MNCV, turmeric was also shown to increase MNCV, indicating nerve recovery. The beneficial effect of turmeric on motor functional recovery was further evidenced by higher SFI values in curcumin-treated diabetic rats (Ma et al. 2016).

In diabetes mellitus, the pathological involvement of the PNS is very broad and often quite severe. The diagnosis of DPN is based on the characterization of the clinical picture with the most typical clinical symptoms and signs and the performance of neurological tests. The main clinical manifestations of somatic impairment are numbness or burning in the lower limbs, tingling, twinges, shocks, needles in the legs and feet, discomfort or pain to the touch of sheets and blankets, and complaints of decreased or loss of tactile, thermal or painful sensitivity (Oliveira & Júnior 2018).

The mechanisms responsible for the beneficial effect of turmeric on DPN appear to be related to improved glycemic control (Adhikari et al. 2015), decrease in oxidative stress (Gondim et al. 2018), and reduction in P2Y12 receptor expression in glial cells in the dorsal root ganglion, which is associated with a decrease in mechanical and thermal hyperalgesia (Oliveira & Júnior 2018). Turmeric has protective action on β pancreatic cells, promotes decreased insulin resistance, increased glucose uptake by increased GLUT4 expression, and increased glycogen storage in the liver (Abd Allah & Gomaa 2015, Adhikari et al. 2015).

Furthermore, curcumin improves glucose homeostasis and promotes an increase in plasma insulin levels, thereby activating glycolysis and inhibiting gluconeogenesis and lipolysis enzymes (Abd Allah & Gomaa 2015). These effects on glucose metabolism may lead to improved glycemic control, and consequently attenuation of neuropathic lesions (Adhikari et al. 2015). Curcumin also can react with reactive

Table IV. Quality evaluation of the included papers according to the SYRCLE scale.

Author/Year	Selection bias			Performance bias		Detection bias		Conflict bias	Report bias	Other source of bias
	1	2	3	4	5	6	7	8	9	10
Ceyhan et al. 2018	L	L	?	L	?	?	?	?	L	L
Daugherty et al. 2018	L	L	?	L	?	?	?	?	L	L
Jia et al. 2018	L	L	?	L	?	?	?	L	L	L
Pierreti et al. 2017	L	L	?	L	?	?	?	?	L	L
Liu et al. 2016a	L	L	?	L	?	?	?	L	L	L
Liu et al. 2016b	L	L	?	L	?	?	?	?	L	L
Ma et al. 2016	L	L	?	L	?	?	?	L	L	L
Abd Allah & Gomaa 2015	L	L	?	L	?	?	?	L	L	L
Adhikari et al. 2015	L	L	?	L	?	?	?	?	L	L
Agthong et al. 2015	L	L	?	L	?	?	?	?	L	L
Babu et al. 2015	L	L	?	L	?	?	?	L	L	L
Greeshma et al. 2015	L	L	?	L	?	?	?	L	L	L
Meng et al. 2015	L	L	?	L	?	?	?	?	L	L
Yuce et al. 2015	L	L	?	L	?	?	?	L	L	L
Cao et al. 2014	L	L	?	L	?	?	?	L	L	L
Zhao et al. 2014a	L	L	?	L	?	?	?	L	L	L
Zhu et al. 2014	L	L	?	L	?	?	?	L	L	L
Zanjani et al. 2014	L	L	?	L	?	?	?	L	L	L
Zhao et al. 2014b	L	L	?	L	?	?	?	?	L	L
Nagilla et al. 2014	L	L	?	L	?	?	?	L	L	L
Banafshe et al. 2014	L	L	?	L	?	?	?	H	L	L
Jeon et al. 2013	L	L	?	L	?	?	?	L	L	L
Joshi et al. 2013	L	L	?	L	?	?	?	L	L	L
Li et al. 2013	L	L	?	L	?	?	?	L	L	L
Ma et al. 2013	L	L	?	L	?	?	?	L	L	L
Mohammadi et al. 2013	L	L	?	L	?	?	?	L	L	L
Kandhare et al. 2012	L	L	?	L	?	?	?	L	L	L
Patzkó et al. 2012	L	L	?	L	?	?	?	L	L	L
Zhao et al. 2012	L	L	?	L	?	?	?	?	L	L
Sharma et al. 2007	L	L	?	L	?	?	?	L	L	L

L – low risk of bias; H – high risk of bias; ? uncertain risk of bias; 1- Allocation series: The control and intervention groups (which received turmeric derivatives) of all articles were randomly assigned; 2- Background: The control and intervention groups of all articles developed peripheral neuropathy, which is due to Diabetes mellitus, sciatic nerve injury, or other methods for the development of neuropathy; 3 - Allocation concealment: Among the articles studied, none described if there was concealment in the designation of the control and intervention groups; 4 - Random accommodation: The control and intervention groups were randomly distributed among the accommodations being exposed to the same conditions; 5 - Blinding: For all articles, none described whether the researcher was aware of which animals received turmeric or the substances used for control; 6 - Random outcome assessment: No article described whether the outcome assessment of the control and intervention groups was performed randomly; 7 - Blinding: For all articles, none described whether the researcher was aware about which animals received turmeric or the substances used for control in the outcome assessment; 8 - Result of incomplete outcome: In nine articles the author does not state whether the same number of animals is used until the outcome and in one article in the outcome has fewer animals than at the beginning of the study; 9 - Selective outcome report: There was no selective outcome report for results that were significant in any of the articles; 10 - Other sources of bias: No article presented other sources of bias.

oxygen species and induce various antioxidant proteins, which have a protective effect on peripheral nerves (Abd Allah & Gomaa 2015). A preclinical study further suggested that turmeric may promote activation of opioid receptors, resulting in an antinociceptive effect (Banafshe et al. 2014).

Sciatic nerve injuries are common causes of lower limb pain and limitation. Detailed knowledge of nerve anatomy is essential for the recognition of alterations and diseases with sciatic nerve involvement. Clinically, sciatic nerve lesions or diseases manifest with pain of varying intensity in the lower lumbar region, with irradiation to the gluteal region and the posterior region of the ipsilateral lower limb. Sensitivity changes and/or motor deficits may be associated (Agnollitto et al. 2017). In all studies included in this systematic review that evaluated sciatic neuropathy, except for one report (Ceyhan et al. 2018), turmeric improved mechanical and painful sensitivity, indicating sciatic nerve recovery. One study (Mohammadi & Mahmoodi 2013) also observed an increase in SFI and four studies (Ma et al. 2013, Mohammadi & Mahmoodi 2013, Yuce et al. 2015, Ma et al. 2016) found an increase in MNCV, corroborating the effect of turmeric promoting sciatic nerve recovery.

Among the proposed mechanisms for the beneficial effect of turmeric in the treatment of sciatic neuropathy are the antinociceptive, antioxidant, and anti-inflammatory effects (Zhu et al. 2014). Curcumin has antinociceptive activity, possibly through its inhibitory action on extracellular signal-regulated kinases. (SRK) and c-Jun N-terminal kinase (JNK) in the dorsal root ganglion. SRK has been shown to play a role in persistent hyperalgesia and JNK is rapidly activated in response to environmentally stressful stimuli. Curcumin treatment during the early stages of peripheral neuropathy may prevent the development of chronic neuropathic pain (Jeon et al. 2013).

In curcumin-treated animals, serum levels of cyclooxygenase 2 have been reduced, which is associated with decreased inflammation and pain (Zanjani et al. 2014). Furthermore, curcumin has a neuroprotective effect and ensures functional recovery in sciatic nerve structures (Yuce et al. 2015).

Chemotherapy-induced painful peripheral neuropathy is a common side effect of antineoplastic treatment with vinca alkaloids, platinum antitumor complexes, taxanes, and other chemotherapeutic drugs, affecting up to 30 to 40 % of patients. Symptoms usually begin when chemotherapy is in place and tend to improve after completing therapy. However, in 25 to 30 % of patients who have pain or paresthesia, these remain or even increase after the end of chemotherapy treatment (Babu et al. 2015).

Vincristine and cisplatin are anticancer drugs widely used in clinical practice (oncology). However, peripheral neuropathy is one of the major side effects of these medicines and may lead to cessation of treatment and poor quality of life (Agthong et al. 2015, Babu et al. 2015). In all studies included in this systematic review in which neuropathy was caused by the adverse effect of vincristine and cisplatin drugs, turmeric improved sensitivity to mechanical and painful stimuli.

The beneficial effects of turmeric on vincristine and cisplatin-induced peripheral neuropathy can be attributed to multiple actions including antinociceptive, anti-inflammatory, calcium inhibitory action, tumor necrosis factor alpha (TNF-α) inhibition, neuroprotective, and antioxidant activity (Greeshma et al. 2015). Turmeric also promotes a reduction in oxidative stress, which is associated with a significant decrease in lipid peroxidation and nitric oxide

and an increase in endogenous antioxidant enzymes (Agthong et al 2015).

Peripheral alcohol neuropathy is a disease associated with chronic alcohol abuse and is characterized by PNS injury. It can affect nerves anywhere in the body, most often in the feet and hands (Silva et al. 2020). In all studies included herein in which neuropathy was caused by alcoholism, turmeric promoted an improvement in sensitivity to mechanical and painful stimuli. In addition, one study (Kandhare et al. 2012) reported an increase in MNCV in alcohol-induced neuropathy. The protective effects of curcumin can be attributed to the reduction of oxidative stress (reduction of malondialdehyde, nitric oxide and calcium level), inhibition of inflammatory cytokines TNF-α and interleukin beta (IL-1β), and impairment of DNA fragmentation in nuclei of the sciatic nerve (Kandhare et al. 2012).

In the preclinical trials included the duration of treatment with turmeric and the animal species employed varied widely between studies, which are a limitation of this systematic review. Different types of turmeric derivatives were also used, with curcumin being the most common phytochemical, but it has limited oral absorption, interfering with bioavailability (Agthong et al. 2015). To improve this pharmacological aspect, strategies such as curcumin in encapsulated nanoparticles, curcumin nanovesicles in the polymeric matrix of PLGA, and turmeric in a SNEDDS nanoemulsion system were developed.

Even in the face of variations between the studies, their results were similar, as all except three (Patzkó et al. 2012, Daugherty et al. 2018, Ceyhan et al. 2018), found a beneficial effect of curcumin on mechanical and thermal sensitivity and nerve recovery in different types of neuropathies. Of these three studies that found no beneficial effect of turmeric, one was unique using the mouse model mutated in the R98C gene to induce type 1B Charcot-Marie-Tooth disease and another was unique in that it used the turmeric derivative J147, which may have contributed to the divergent results of these studies. This derivative can improve acute and transient pain sensitivity, which does not seem to be sufficient to significantly improve MNCV (Daugherty et al. 2018).

Another limitation of this systematic review is the variation between studies regarding the means of induction of different PN in animals. While in some studies animals in the intervention group developed thermal or mechanical hyperalgesia, in others they developed thermal or mechanical hypoalgesia. However, regardless of whether induced neuropathy is characterized by hyperalgesia or hypoalgesia, turmeric was able to improve neuropathy by promoting lower thermal or mechanical sensitivity in animals that developed hyperalgesia and increased sensitivity in those that developed hypoalgesia.

Behavioral methods for assessing neuropathy also varied among the studies included in this systematic review. Thermal sensitivity evaluation was performed by means of HPT, PT, CPT, CAT and PT plus zymosan, whereas VFFS, TFT, RST, FT, RRT and TBT were used to assess mechanical sensitivity. Some studies have even evaluated the MNCV, SFI, SNFR and SNSI. Regardless of the behavioral method employed in the different studies, a beneficial effect of turmeric on thermal or mechanical sensitivity and nerve recovery was observed. Only one study (Daugherty et al. 2018) found no improvement in MNCV in animals with DPN, one study (Ceyhan et al. 2018) found no improvement in sensitivity to thermal and mechanical stimuli in sciatic neuropathy, and one study found no improvement in the RRT in the type 1B Charcot-Marie-Tooth disease animal model (Patzkó et al. 2012).

The impossibility of performing the meta-analysis and the absence of clinical trials on the

subject were other limitations of this systematic review. From the thirty articles selected for this systematic review, only eight (Ma et al. 2016b, Adhikari et al. 2015, Agthong et al. 2015, Cao et al. 2014, Joshi et al. 2013, Ma et al. 2013, Mohammadi & Mahmoodi 2013, Kandhare et. al. 2012) numerically described the values of the control and intervention groups, and there was disagreement regarding the type of neuropathy and/or neuropathy assessment methods between such studies. Hence, the outcomes were not measured in a similar enough way to be properly mathematically combined, which made it impossible to perform meta-analysis.

Even with some limitations, the large number of studies included in this systematic review and the agreement of the results of these studies make it possible to infer that turmeric had a beneficial effect on the treatment of PN in animal models. Furthermore, an asset to be considered is that all included articles were recently published and have good methodological quality, because the risk of biases analyzed using the SYRCLE scale was low or uncertain. Considering the divergences in the literature on the efficacy of turmeric for the treatment of PN, this systematic review, which was conducted with many pre-clinical trial studies, may contribute to the expansion of knowledge regarding the potential of this herbal medicine as a treatment of diseases related to PN, such as diabetes mellitus.

CONCLUSIONS

Turmeric derivatives demonstrated a valuable improvement on the outcomes of PN in animal models, regardless of the cause, especially in DPN and sciatic neuropathy. Further studies are still required to validate the therapeutic benefits of turmeric derivatives in chemotherapy induced PN and alcoholic induced PN. This systematic review does contribute to the state of the art of phytotherapy by: i) supporting the conduction of clinical trials to verify the possible application and feasibility of these treatments in humans as an alternative or adjunct to current pharmacological therapy; ii) endorsing the rational use of turmeric and its derivatives in the treatment of diseases related to diabetes mellitus; and iii) reinforcing the potential of herbal medicines as a health promotion strategy at the basic level.

Acknowledgments

The authors greatly thank the Universidade Federal de São João Del Rei and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for the financial support (code 001).

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How to cite

SILVEIRA RS, BALDONI AO, COUTO RO, MENDONÇA TS & DOMINGUETI CP. 2023. *In vivo* efficacy of turmeric (*Curcuma longa* L.) in the treatment of peripheral neuropathy: A systematic review of animal models. An Acad Bras Cienc 95: e20200447. DOI 10.1590/0001-3765202320200447.

Manuscript received on March 31, 2020;
accepted for publication on January 18, 2021

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