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Systematic review: Medicinal use and scientific elucidation of the *Piper* genus for the treatment of symptoms and inflammatory diseases

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The aim of this study was to conduct a systematic review that reported the medicinal use of the genus *Piper,* and pharmacological elucidations for the treatment of symptoms and processes of inflammation and inflammatory diseases. The systematic review was prepared in accordance with PRISMA guidelines. The databases used for this research were the Web of *Science* and Scopus, where associations with the terms were applied in both databases: "*Piper*" *and* "*Ethnobotanical*" and "*Piper*" *and* "*Anti-inflammatory effect*". Initially, the research identified 153 articles, of which 24 articles were selected for final analysis following the inclusion criteria. The results indicate that the medicinal use of species of the *Piper* genus entails mainly using of leaves, roots, and fruits, and decoct, maceration and powder for the treatment of inflammatory and respiratory diseases such as asthma and bronchitis. Regarding the evaluation of the anti-inflammatory effect of the genus, only seven species presented studies with their scientifically proven anti-inflammatory effect. Biases in the methodology applied in the studies were observed. In this systematic review, it was noticed that both studies addressed have gaps that can cause damage to future research and that pharmacological studies for inflammation with the use of the species themselves are still limited, with a more job for the isolated compounds of these plants.

Key words: *Piper, medicinal,* ethnobotanic, anti-inflammatory effect.

INTRODUCTION

Piper genus is the most representative of Piperaceae family, composed of about 1,000 species (Durant-Archibold et al., 2018), and has wide distribution on temperate regions from both hemispheres (tropical and sub-tropical). It is used for cooking, and has aromatic, ornamental and medicinal purposes (Reigada et al., 2007; Santos et al., 2012). In Brazil, it can be found from North to South, where 292 species occur, of which 44 are

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variety and 184 are endemic (Flora do Brasil, 2018).

Concerning the botanical aspects, these genus specimens appear as sub-shrubs, shrubs or trees, measuring from 1 to 5 meters; they are able to reach up 10 meters in height. The stems are usually lignified, knotty and have many branches. Leaves have a long petiole and alternate with the stem. The limbo is simple, having its entire margin, with different shapes and sizes. The flowers are sessile, arranged in spikes opposite to leaves, varying in length and thickness, upright, sub-curved or curved; they are accompanied by thin or thick peduncles, of 2 to 5 stamens and 3 to 4 stigmas, filiform, curved, styled or sessile. The ovary is ovoid or sub-ovoid. Fruits are globular drupe with little thickened pericarp (Reitz, 2003; Guimarães and Giordano, 2004).

Ethnobotanical studies in the literature exhibit the genus *Piper* related to medicinal use in tea forms (decoction), infusion and aromatic baths (Blumenthal, 1998; Santhakumari et al., 2003; Wirotesangthong et al., 2008). It is mostly species used in traditional medicine for treating gastrointestinal diseases, hypertension, anti-hemorrhagic, diuretic, pain and inflammation (Gupta et al., 2015; Reigada et al., 2007; Roersch, 2010).

Species of this genus produce compounds with diverse biological and pharmacological properties, such as anxiolytic, analgesic, anti-inflammatory, vasodilatory, cytotoxic, immunomodulatory, antimicrobial, antifungal and promising antitumor activities (Bezerra et al., 2008; Rodrigues et al., 2009; Moraes et al., 2011; Raj et al., 2011). In this sense, phytochemistry contributes to verifying *Piper* genus biological activities cited in the ethnobotanical researches (Parra et al., 2011).

Phytochemical research brings about numerous scientific studies in many parts of the world, which has led to isolation of several bioactive compounds such as kavalactones (Xuan et al., 2008; Whitton et al., 2003), aristolactams (Cardoso Júnior and Chaves, 2003; Chaves et al., 2006), phenylpropanoids (Chaves and Santos, 2002), lignoids (Chen et al., 2007; Bodiwala et al., 2007), chromones (Morandim et al., 2005), terpenes (Baldoqui et al., 2009; Péres et al., 2009), steroids (Parmar et al., 1997), prenylated benzoic acids (Lago et al., 2009; Chaves et al., 2010) and amides (Araújo-Júnior et al., 1997; Chaves et al., 2003; Srinivasan, 2007; Cotinguiba et al., 2009). These characterize the metabolites of this genus. The first isolated amide of the Piper genus was piperine (Lee et al., 1984).

The main biological activities attributed to isolated substances are antifungal, insecticidal, bactericidal, antitumor, trypanocidal, antiparasitic, antimicrobial, antiprotozoal, anti-inflammatory, antinociceptive and antioxidant (Pohlit et al., 2004; Nakamura et al., 2006; Deshwal, 2013; Zakaria et al., 2010; Agbor et al., 2012).

A striking feature of the genus is presence of rich oil content in its structures, especially in leaves and fruits (Albiero et al., 2005). It has essential oils with chemical constituents such as monoterpenes, sesquiterpenes, arylpropanoids, aldehydes, ketones, and long-chain alcohols. This shows its commercial and industrial potential, as well as use in traditional medicine (Correa et al., 2011)

Some studies of scientific reviews on species and isolates from *Piper* genus have already been published (Roersch, 2010; Gutierrez et al., 2013; Monzote et al., 2017, Durant-Archibold et al., 2018); however, there is no systematic review of the genus *Piper* focusing on inflammatory processes. Hence, this review aims to report the medicinal use of *Piper* genus, including pharmacological elucidation for the treatment of symptoms of inflammation and inflammatory diseases.

MATERIALS AND METHODS

Research strategy

The systematic review was performed according to PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). It consists of a 27 items checklist and a flow diagram that instructs articles search and selection in four steps - identification, selection, eligibility and inclusion - for authors to contribute to the quality and reliability of the review in question (Moher et al., 2009).

The study was guided by two questions. Ffirst: "Which species of *Piper* genus are used empirically by population for symptoms of inflammation and inflammatory diseases treatment"? The second: "Which species of the genus *Piper* have scientifically elucidated anti-inflammatory effects?"

The articles mentioned in the review were publications available from January 2003 to July 2017. For this research, the Web of Science and Scopus databases were used, where the following association of terms was applied in both bases: "*Piper*" and "Ethnobotanical", "*Piper"* and Anti-inflammatory effect. The constancy of the terms aims to guarantee greater trustworthiness in search application forms and later comparison of the publication date.

The inclusion and exclusion criteria were applied to both consulted databases. Inclusion criteria: articles published in full text, in English language and that portray the subject by means of the association of the above-mentioned terms. Exclusion criteria: duplicate articles, comparative, inconclusive, or dubious studies. After the use of research criteria, certification of selected productions was carried out, using a meta-synthesis type qualitative approach.

Studies selection

Two independent researchers (C.N.F.L. and L.F.L) made studies research and selection. The choice of articles was made by reading title and abstract, with the application of an evaluation formulary with eligibility criteria. Later, publications were evaluated by complete reading. This step is indispensable to ratify the inclusion criteria. Any divergences were agreed on between the two researchers.

Methodological quality analysis/studies' bias risk

The studies were evaluated using SYRCLE's RoB (Hooijmans et al., 2014) tool, for pre-clinical *in vivo* studies, with non-human animals. Related to ethnobotanical and pre-clinical studies *in vitro* it

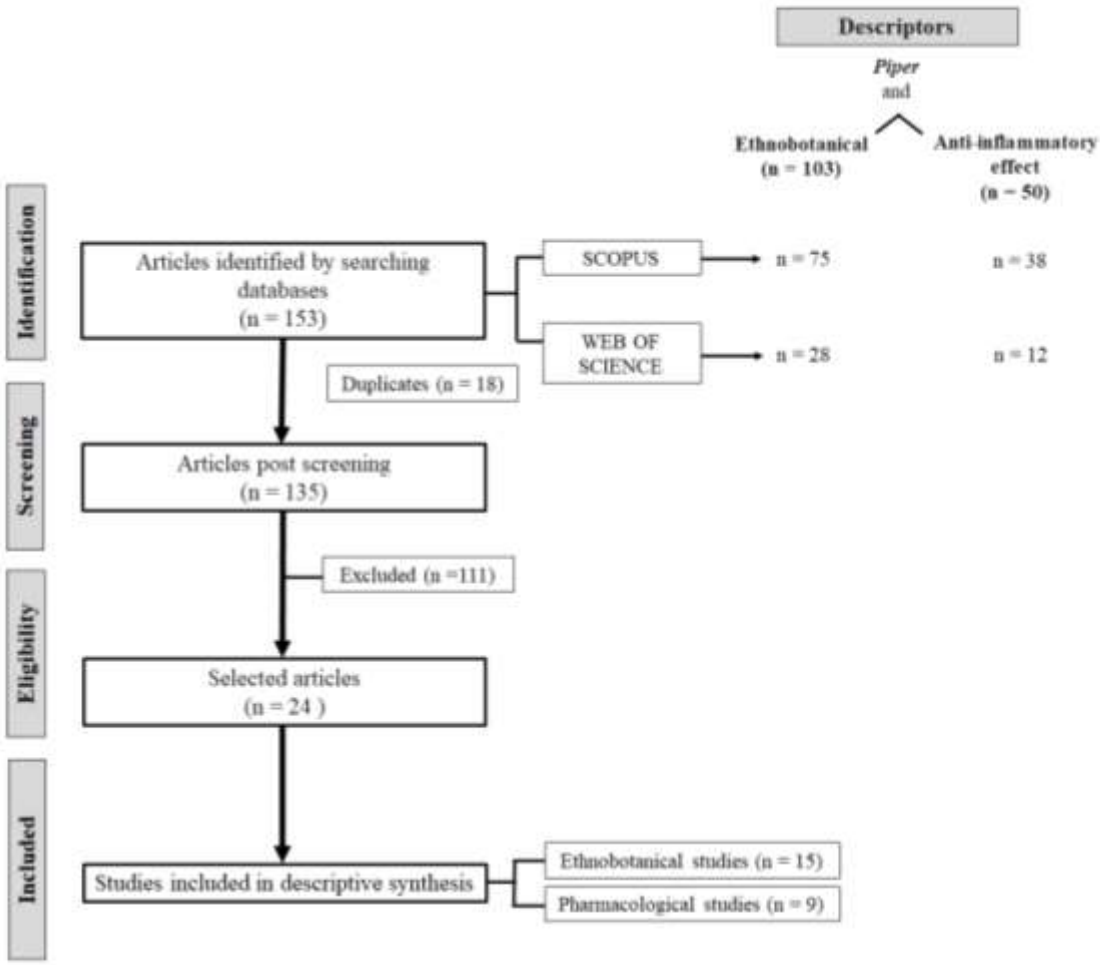

Figure 1. Selected research and results.

was not possible to carry out this analysis, once there is no validated tool for such finality.

SYRCLE's RoB tool was elaborated based on Cochrane Collaboration's (Higgins and Green, 2011) criteria, being adapted to evaluate the methodological quality and bias risks of experimental studies with non-human animals. This tool is composed of 10 entries that are related to 6 bias types: selection bias, performance bias, detection bias, friction bias, bias notification and other bias (Hooijmans et al., 2014). Based on the aforementioned tool, the studies were classified as "low bias risk", "high bias risk" and "not clear bias risk".

Extraction and data analysis

Data were obtained by one of the researchers (C.N.F.L.) using a list of selection criteria, which were accurately verified by the second researcher (L.F.L.). Regarding the articles that deal with ethnobotanical studies, the extracted items were information related to the species, the structure used, the form of use, traditional use, and the country. Regarding ethnopharmacological studies, the information obtained was: species, the structure used, type of extract/essential oil, type of test and effect, according to the literature. Grouping statistics (meta-analysis) were not possible due to methodological heterogeneity between studies.

RESULTS

In this systematic review, were found 153 articles in consulted databases. In the Scopus database, there were 113 articles and in Web of Science, 40 articles. After abstracts and titles screening were excluded 18 duplicated articles, remaining 135, and from full-text analysis, 111 texts were excluded. Finally, after inclusion and exclusion criteria application, 24 articles were selected for this study, in which 15 articles addressed ethnobotanical studies that demonstrated *Piper* species use in traditional medicine for inflammation and 9 articles with pharmacological studies of the species demonstrating elucidation for this activity (Figure 1).

Medicinal use of *Piper* genus species

Studies have demonstrated *Piper* genus use in traditional medicine. Here we highlight some ethnobotanical surveys that exhibit *Piper* species use for the treatment of inflammatory diseases.

These species are widely used as a medicinal plant mainly in countries like Indonesia and India, in which a greater number of works were observed. The medicinal genus use occurs by the usage of all parts of the plant; leaves, roots, and fruits were the most used; and the forms of predominant uses in the studies were decoction, maceration, and powder use. However, some studies did not report both. About traditional species used for the treatment of symptoms caused by inflammation, inflammatory processes and inflammatory diseases, the prevalence of the treatment of respiratory diseases such as asthma and bronchitis was evidenced. Other medicinal uses are for rheumatism and gout, diseases considered inflammatory, and for the treatment of inflammatory processes such as wound healing, skin allergies and gastrointestinal ulcers. The symptoms of inflammation are fever and cough (Table 1).

Scientific elucidation of anti-inflammatory activity of *Piper* genus species

Related to the evaluation of the anti-inflammatory effect of the *Piper* genus, this systematic review showed that many species that already have medical use by population have not yet had their effects scientifically validated. According to research, only seven species have worked with their scientifically proven anti-inflammatory effect. The most commonly used plant part was leaves, the extract being the most predominant preparation form. Only two works are related to essential oil use. Related to the pharmacological test type used to evaluate the anti-inflammatory activity, paw edema, and pleurisy models were the most used (Table 2).

Methodological quality/bias risk

In Figures 2 and 3, all pre-clinical studies with non-humans animals were evaluated and classified as low bias risk (100%) based on the questions, if the evaluator did not have previous knowledge of results, if identification of incomplete results was adequate, if studies were free of selective results and if they were free of other problems that would cause bias.

DISCUSSION

Since primitive civilizations, man has been intimately related to plants in order to grow his own food and medicine. The popular medicinal use of plants is an ancient art based on the accumulation of information passed through successive generations (Zardo et al., 2016). Thus, ethnobotanical knowledge provides the pharmacological and industrial applications. From popular wisdom about this type of plant that several research centers seek to prove the effectiveness of certain medicinal plants (Albuquerque, 2005).

In the present study, among the ethnobotanical studies reported for medicinal *Piper* genus use for inflammatory diseases, thirteen species were cited. In view of the analyzed studies, it can be seen that *Piper* species are used for different medicinal purposes and that often the vegetal part used, the form of use and medicinal application of a species can vary according to the cultural scene.

When comparing Tables 1 and 2 that demonstrate medicinal use and pharmacological elucidation, respectively, of this genus species, it can be verified that despite the report in the ethnobotanical studies few of these species had scientific elucidation confirmed in the area of the inflammation. The species that were scientifically elucidated and at the same time have reports of medicinal use by the population according to this systematic review were: *Piper umbellatum*, *Piper nigrum* and *Piper sarmentosum*.

People use *P. umbellatum* to treat fever and tissue cicatrization (Akendengue et al., 2005; Silalahi et al., 2015). Iwamoto et al. (2015), in their study, evaluated the anti-inflammatory activity of dichloromethane extract, from leaves of this species, on paw edema and carrageenan-induced peritonitis models; they observed decreased inflammation, and leukocyte migration.

P. nigrum is traditionally used to treat sore throat, fever, asthma, and cough (Albuquerque et al., 2007; Silalahi et al., 2015; Sureshkumar et al., 2017; Suroowan and Mahomoodally, 2016). Tasleem et al. (2014) elucidated the anti-inflammatory effect of this species in carrageenan-induced paw edema models that exhibited a significant decrease in edema at different concentrations of hexane and ethanolic extracts. Ahmed et al. (2013) demonstrated that the methanolic extract of this species significantly improves the cholinergic and characteristic neurodegeneration-induced dysfunction of Alzheimer's disease.

Ethnobotanical studies with *P. sarmentosum* reported the popular use for rheumatism and gout (Li et al., 2016) and its action for inflammation was elucidated by Lee et al. (2011) who demonstrated that the methanolic extract of this species reduced the production of nitric oxide (NO), which is one of the markers in one of the inflammation pathways (Gonçalves et al., 2000).

Kim et al. (2017) by means of tests aimed the inflammation ways of nitric oxide (NO) and prostaglandins (PGE_2) and the measurement of genes that trigger inflammatory processes; the methanolic extract of *P. attenuatum* exerted anti-inflammatory effects in *in vitro* tests with macrophage cells.

The other ten *Piper* species cited in Table 1 do not have a scientific elucidation approach to inflammation yet, according to databases used. The species are the following: *P. betle, P. marginatum, P. acutifolium, P.*

Table 1. Medicinal use of *Piper* species to treat symptoms of inflammation and inflammatory diseases.

Scientific name	Parts use	Method of preparation	Medicinal use	Country	Reference
Piper acutifolium Ruiz & Pav.	Leaves	Decoction	Gastritis	Peru	De Feo (2003)
Piper betle L.	Leaves	Decoction and maceration	Ulcer	China	Li et al. (2016)
	Leaves	Liquid extract	Asthma	India	Savithramma et al. (2007)
	Leaves	NR	Febrifuge	Indonesia	Silalahi et al. (2015)
	Whole plant	Powder (taken orally)	Bronchitis and cough	India	Sureshkumar et al. (2017)
	Leaves	Decoction	Sore throat Skinallergies	Indonesia	Sujarwo et al. (2015)
	Leaves	Juice (taken orally) Maceration (Used over the chest) Maceration (taken orally) Chewed	Cough Asthma Respiratory disorders Bronchitis	Africa	Suroowan and Mahomoodally (2016)
Piper cubeba Vahl.	Fruit	NR	Rheumatism	Indonesia	Silalahi et al. (2015)
Piper guineense Schumach. & Thonn.	Fruits Whole plant	Decoction Powder Balsam	Asthma	Africa	Gbekley et al. (2017)
Piper hancei Maxim.	Roots	Decoction	Gastritis, osteitis	China	Li et al. (2016)
Piper longum L.	Immature fruits and roots	Powder of roots mixed with honey (taken orally) Decoction Immature fruits and roots (taken orally)	Asthma	India	Savithramma et al. (2007)
	Fruit	NR	Rheumatism	Indonesia	Silalahi et al. (2015)
		Powder (taken orally)	Cough	India	Sureshkumar et al. (2017)
Piper marginatum Jacq.	Roots, leaves, stem	NR	Asthma	Brazil	Albuquerque et al. (2007)
Piper nigrum L.	Seeds	NR	Sore throat	Brazil	Albuquerque et al. (2007)
	Seeds	NR	Febrifuge	Indonesia	Silalahi et al. (2015)
	Roots	Powder (taken orally)	Asthma	India	Sureshkumar et al. (2017)
	Fruits	Powder (taken orally)	Cough	Africa	Suroowan and Mahomoodally (2016)
Piper peltatum L.	NR	NR	Skin problems, processes "granos"	Guatemala	Hitziger et al. (2016)
Piper sarmentosum Roxb.	Leaves and roots	Decoction and maceration	Rheumatism, gout	China	Li et al. (2016)
Piper tuerckheimii C.DC.	NR	NR	Fever and woundhealing	Guatemala	Hitziger et al. (2016)
	Leaves	NR	Inflammation,"loss of senses"	Guatemala	Michel et al. (2016)
Piper umbellatum L.	NR	Used on the skin	Febrifuge, Cicatrizant	Africa	Akendengue et al. (2005)
	Leaves	NR	Febrifuge	Indonesia	Silalahi et al. (2015)

NR, Not reported.
Source: Research data (2017).

*haucei, P. tuerckheimii, P. peltatum, P. longum, P. cubeba*e *P. guineense*. This shows the scarcity of studies that evaluate the anti-inflammatory activity of these species, but there are reports of genus

Table 2. Scientific elucidation of anti-inflammatory effect of species of the *Piper* genus.

Scientific name	Parts use	Type of extract/oil	Type of test	Effect	Reference
Piper aleyreanum C.DC.	Leaves	Essential oil	Pleurisy induced by carrageenan	The treatment with essential oil de *P. aleyreanum* reduced the main features of acute inflammation, including exudation and leukocyte number, mainly by a reduction in neutrophil differential cell count in the pleural cavity. Oil essenctial treatment (1-30 mg/kg, p.o.) caused a dose dependent reduction mainlyin ethanol-induced gastric lesions, decreasing the ulcer area mainly at doses of 10 and 30 mg/kg, with a mean ID50 value of 1.7 (0,9–3,1) mg/kg and an inhibition of 8774% at 10 mg/kg. Similarly, the essential oil via i.p. (10 mg/kg) reduced by 44,8712,8% gastric lesions induced by etanol.	Lima et al. (2012)
	Stem		Acute gastric lesions	The methanolic extract *P. attenuatum* Pa-ME Suppressed the Production of NO in macrophage stimulated with lipopolysaccharides, pam 3CSK4-and poly (I: C). The expression levels of mRNA and NO inducible synthetase (iNOS) and cyclooxygenase 2 (COX-2) were decreased. It reduced the translocation of p50 / NF-κB and AP-1, as well as the activity of its enzymes Src, Syk and TAK1.An immunoprecipitation analysis was turned to the binding between its substrates which were induced by Src, Syk and TAK1 overexpression were also reduced. The methanolic extract of *P. attenuatum* exerts anti-inflammatory effectao by directing Src and Syk on the signaling path NF-κB and TAK1 on the signaling path AP-1.	
Piper attenuatum Buch.-Ham. Ex Miq.	NR	Methanolic extract	NO and PGE_2 Production Assay; Measurement of mRNA Expression Levels by Reverse- Transcriptase Polymerase Chain Reaction (RT-PCR).	The extract at the dose of 150 mg/kg decreases the TNF-a serum levels in Wistar rat with atherosclerosis by around 45.63%.	Kim et al. (2017)
Piper crocatum Ruiz & Pav.	Leaves	N-butanol	Decrease of TNF-α level and decrease of IL-6 levels pre and post-test	Inhibition of inflammatory mediators including TNF- α, IL-1, IL-6, and NO on LPS-induced macrophage cells.	Wahjuni et al. (2016)
P. nigrum L.	Leaves	Ethanolic extract	Pro-inflammatory activation of cells; Measurement of TNF-α, IL-β e IL-6; Concentration and inhibitory activity assay; Measurement of nitrite associated with NO concentration and inhibitory activity assay.	The hexane extract showed anti-inflammatory activity at a dose of 5 and 10 mg/kg compared to control, but less than the standard. The hexane extract exhibited maximum anti-inflammatory effect at a dose of 10 mg/kg after 60 min. The ethanol extract showed good anti-inflammatory activity at dose of 10 mg/kg as compared to control but less activity at all doses as compared to standard drug. The ethanol extract exhibited maximum activity at a dose of 10 mg/kg after 60 min.	Laksmitawati et al. (2017)
	Fruits	Ethanol extract and hexane	Carrageenan-Induced paw edema	The treatment with methanolic extract of *P. nigrum* L., only dose of 187.5 mg / kg reduced the serum AchE activity in the brain by 22.9%. However, both doses tested (187.5 mg/kg and 93.75 mg/kg) presented significance in CRP levels (-28.41% -25.90% 187.5 mg/kg b.w./-27.16%, -23,12% 93.75 mg/kg b.w.), NF-κB_{65} (-37.86%, -17.52% 187.5 mg/kg b.w./-36,22%, -16,92% 93.75 mg/kg b.w.) e MCP-1, (-40.8%, -19.47% 187.5 mg/kg b.w./-35.57%, -17.27% 93.75 mg/kg b.w.). Thus, extract significantly improves the cholinergic dysfunction and neurodegeneration induced by AD inflammation.	Tasleem et al. (2014)

Table 2. Contd.

	Seeds	Methanolic extract	Experimental model of Alzheimer's disease induced by $AlCl_3$	The methanolic extract of *P. sarmentosum* (100, 50 and 25 µg / mL) reduced the production of nitric oxide in 62.82 ± 1.53, 46.53 ± 1.15 and 26.83 ± 1.73 respectively.	Ahmed et al. (2013)
Piper sarmentosum Roxb.	NR	Methanolic extract	Nitrite determination	*P. umbellatum* SDE treatment significantly inhibited the first phase of inflammation, in an independent way, as well as indomethacin 10 mg/kg. SDE was able to inhibit inflammation up to 4.5 hours, period coincident with prostaglandin release, which could suggest an action on prostaglandins production. In the second phase, all SDE doses inhibited inflammation at 48 hours while 400 mg/kg dose also inhibited the second inflammatory peak (72 h). This result suggests an effect on neutrophil mobilization, quite similar to the corticosteroids effects that efficiently inhibit the cellular phase of inflammation. In the carrageenan-induced peritonitis model, leukocytes migration in the negative control group was 14160±1705 cells/mL and cell migration was inhibited both by dexamethasone (60.5%, 5 mg/kg) and by *P. umbellatum* SDE (52.0%, 200 mg/kg).	Lee et al. (2011)
Piper umbellatum L.	Leaves	Dichloromethane extract	Paw edema and pleurisy induced by carrageenan	The groups treated with oil essential of *Piper vicosanum* (OPV) doses of 100 and 300 mg/kg showed a significant decrease in edema at the four hours of observation. The inhibitions were 78±2% and 75±3% after 2 h and 80±2% and 86±3% after 4 h, respectively. Additionally, the oral administration of OPV significantly inhibited the leukocyte migration at all doses tested (100 and 300 mg/kg), with inhibitions of 70±3% and 85±2%, respectively, and higher inhibition at a dose of 300 mg/kg.	Iwamoto et al. (2015)
Piper vicosanum C.DC.	Leaves	Essential oil	Paw edema and pleurisy induced by carrageenan		Brait et al. (2016)

NR, Not reported.
Source: Research data (2017).

use for inflammation treatment (Moreira et al., 1998; Felipe et al., 2006). In relation to the species *P. vicosanum*, *P. aleyreanum* and *P. crocatum* the opposite occurred; these have scientific elucidation and, nevertheless, were not found articles demonstrating the traditional use through ethnobotanical studies in the databases of Web of Science and Scopus.

Brait et al. (2015) studied *P. vicosanum* through models of paw edema and pleurisy induced by carrageenan; they obtained significant results for the edema reduction and for leukocyte migration in pleurisy. Also, *P. aleyreanum*, its anti-inflammatory effect also was evaluated by the carrageenan-induced pleurisy model and the acute gastric lesion test. Both tests were performed by Lima et al. (2012) and they obtained significant results regarding inflammatory processes reduction.

The studies cited above report the traditional use of this species, *P. aleyreanum*, as immunomodulatory, analgesic and antidepressant (Brait et al., 2015); people use it empirically in a more general way for bronchitis, intestinal pain, skin irritations and inflammation treatment (Lima et al., 2012).

Wahjuni et al. (2016) and Laksmitawati et al. (2017) performed tests with *P. crocatum*. Both evidenced the reduction of serum levels of TNF-α, IL-1, IL-6, and NO in Wistar rats and in LPS-induced macrophage cells, respectively. In these articles, authors do not describe empirical medicinal use; only bioactive components were present in these plants, correlating with its anti-inflammatory activity.

During the research were found several works that investigate the pharmacological activity of isolated compounds from the *Piper* genus for inflammation. Sheikh et al. (1993) isolated triterpenes and β-sitosterol from *P. betle* to plaquetary aggregation study and anti-inflammatory effect; the last one were used the model of paw edema induced by carrageenan to evaluate its potential.

In the species *P. nigrum* and *P. longum* the

Reference	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Kim et al. (2017).	+	+	?	+	?	-	+	+	+	+
Iwamoto et al. (2017).	?	+	-	-	-	-	+	+	+	+
Wahjune et al. (2016).	+	+	?	+	?	-	+	+	+	+
Brait et al. (2015).	?	+	?	?	-	-	+	+	+	+
Tasleem et al. (2014).	?	?	?	+	?	?	+	+	+	+
Ahmed et al. (2013).	+	+	?	+	-	-	+	+	+	+
Lima et al. (2012).	+	+	?	+	?	-	+	+	+	+
Lee et al. (2011).	+	+	?	+	?	-	+	+	+	+

+	**Low risk of bias**
-	**High risk of bias**
?	**Unclear rik of bias**

Figure 2. Methodological quality summary for preclinical trials: review of authors judgments about each methodological quality item for each study included: **P1,** Was the allocation sequence adequately generated and applied?; P2, Were the groups similar at baseline or were they adjusted for confounders in the analysis?; P3, Was the allocation to the different groups adequately concealed during?; P4, Were the animals randomly housed during the experiment?; P5, Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?; P6 - Were animals selected at random for outcome assessment?; P7, Was the outcome assessor blinded?; P8, Were incomplete outcome data adequately addressed?; P9, Are reports of the study free of selective outcome reporting?; P10, Was the study apparently free of other problems that could result in high risk of bias?).

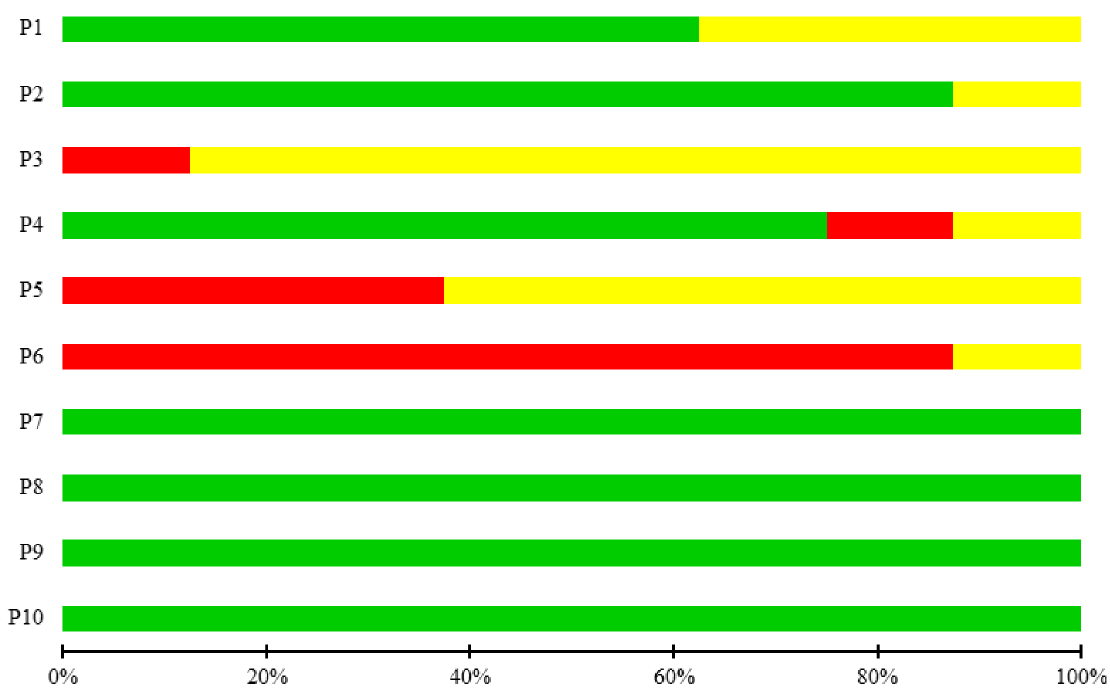

Figure 3. Methodological quality of included studies. Green bars indicate the proportion of articles that present low bias risk; red bars indicate the proportion of studies with high bias risk and yellow bars indicate the proportion of studies with unclear bias risk.

major component is piperine that has biological activities: anti-inflammatory, antioxidant, analgesic, healing, antifungal, antibacterial and facilitates blood circulation activity (Bae et al., 2011; Carnevallia and Araújo, 2015). Liang et al. (2016) evaluated piperine for pyroptosis in murine macrophages using pyroptosis assay. Cruz et al. (2013) studied its application in convulsion by checking deaths number and survivors through pilocarpine-induced seizure tests by the GABAergic system in an animal model. Kim et al. (2012) verified piperine inhibitory action on COX-1 with the COX-2 induction test by 13-acetate 12-myristate-frobol (PMA).

In Web of Science database were found five articles using isolated piperine compound and one with the compound allylpyrocatechol (APC) extracted from *P. betle* species. This component was evaluated by induced production of NO and PGE_2 of lipopolysaccharide (LPS) in murine macrophages cells to verify their anti-inflammatory capacity (Sarkar et al., 2008).

The remaining articles, using piperine, investigate: The apoptosis in neuronal cells and the anti-inflammatory activity in Parkinson's disease induced by 6-OHDA (Shrivastava et al., 2013), the neuro-inflammation on BV_2 microglia induced by inflammatory responses to LPS (Wang-Sheng et al., 2017), the ulcerative colitis by determining TLR4 receptor cholesterol in the pathway of cellular inflammation (Gupt et al., 2015) and the acute pancreatitis induced by cerulein by activation inhibition of mitogenic protein kinase (Bae et al., 2011).

Besides these works, other components such as: N-isobutylamine, (E) -β-caryophyllene (BCP) and other alkaloids were used, respectively, for anti-inflammatory effect of edema in formation in acute analgesia, in a murine model of nephropathy to verify anti-inflammatory properties and in neuroinflammatory processes in Parkinson's disease in the dopaminergic neuronal system (Reynoso-Moreno et al., 2017; Horváth et al., 2012; He et al., 2016).

Other works that approach isolated compounds, were by De León et al. (2002) who studied *P. fimbriulatum* through its furofan lignan (+)-diayangambin isolated component *in vivo* assays such as carrageenan-induced paw edema to verify its immunomodulatory and anti-inflammatory efficacy, and by Chion et al. (2003) which used piperlactam S isolated from *P. kadsura* for chemotaxis treatment by means of chemotactic migration, adhesion, measurement of phagocytic activity and cytokine production assays.

The analysis of the quality of methodology and the risk of bias of the studies inserted in a systematic review is of fundamental importance (Hooijmans et al., 2014). This is because this evaluation demonstrates that the research developed was well planned and carried out efficiently and that the results presented were interpreted correctly and comprehensible (Festing and Altman, 2002). In the articles addressed in this review, biases in the methodology were observed in preclinical studies with non-human animals, mainly in the allocation and blinding of the groups. This data require some special attention since studies that present a risk of methodological bias do not guarantee reliable results.

Conclusion

Studies covered in this systematic review prove that the *Piper* genus includes species with bioactive activities, with great potential for inflammatory disease treatment.

In traditional medicine, ethnobotanical studies showed that leaves, roots, and fruits were most used parts under decoction, maceration and powder form for inflammatory diseases of respiratory tract treatment, such as asthma, bronchitis, and cough. Already in the studies that scientifically validated *Piper* genus anti-inflammatory activity, only seven species presented works with their anti-inflammatory effect scientifically proven.

This review also showed that several ethnobotanical studies still present gaps in relation to detailed information regarding the plant part used and how they are used, as well as other data. The lack of such reports may lead to a loss for future pharmacological research. Thus, it is considered that interviews of this size should be very explanatory, aiming to collect as much information as possible about plant use in traditional medicine.

In the ethnopharmacological studies (*in vivo* or *in vitro*), there was also lack of information, mainly in relation to the plant part used to obtain the extract, implying that the lack of this data may be a reflection of the scarcity of ethnobotanical studies well structured. Another factor to be observed is that the pharmacological studies for inflammation with species use itself are still limited, with a larger number of works for isolated compounds from these plants. The research also did not present any study that reported genus use for clinical trials. In view of this, it can be seen that research with the *Piper* genus as a therapeutic agent in modern medicine is still very scarce, related to anti-inflammatory activity.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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