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**Review Article**

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# Anti-Inflammatory Action of *Spilanthes acmella*: A Systematic Review

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**Abstract** *Spilanthes acmella* known in Brazil as jambu is a typical herb of the northern region of Brazil that has application in traditional medicine to treat toothache, stomatitis and throat diseases, being antiviral, antibacterial, antiseptic, diuretic, anti-inflammatory and healing. Studies included in this systematic review are *in vivo* experiments using mice whose inflammation was obtained with the use of carrageenan introduced into the paw and the decrease of edema was measured by plethysmometry. There was also, *in vitro* experiment using murine macrophages. These studies have recognized that *Spilanthes acmella* has significant anti-inflammatory and analgesic activity. However, additional studies in other models and clinical trials have been recommended to confirm the results and to establish the mechanism of action of the exact as well as the active principles involved in the anti-inflammatory and analgesic activity. Although studies investigating the anti-inflammatory effect of *Spilanthes acmella* are scarce, it is necessary to recognize the biological potential of this species.

**Keywords** *Spilanthes acmella*, anti-inflammatory action, spilanthol

## Introduction

The species *Spilanthes acmella* known in Brazil as jambu is a typical herb of the northern region of Brazil, where it is part of meals of the local cuisine as the tacacá and the duck in the tucupi [1]. In addition to being widely used in cooking, jambu is medicinally important because it has active principles such as essential oil, saponins, spilanthines, phyllosilines, phylloesterina, choline, triterpenoids and, mainly, espilanthol, which had the structure revealed by Yasuda in 1980 [1]. *Spilanthes acmella* is an indigenous herb belonging to the family Compositae. It is grown as an annual herb throughout the tropics. It has conical small yellow flowers. The whole plant is claimed to possess medicinal properties. Spilanthol is the main constituent isolated from many parts of *Acmella oleracea* and has been shown to exert different biological activities [02].

To establish a relationship between the pharmacology and the chemistry of a medicinal plant it is necessary to study its phytochemical components. Several studies were carried out by chemical analysis and structural determination of pungent alamides of *Spilanthes acmella*. The main pungent constituent reported in the *S. acmella* plant is the "spilanthol", which is an isobutylamide and is well known for its larvicidal properties [03].

The flower head part and the plant root were reported to be rich in active principles. Triterpenoids were also found in the plant [04]. Spilanthol has a strong spicy taste, can produce local astringency and anesthetic effects. Other important traditional uses of this herb are the following: treatment of rheumatism, stuttering, paralysis of the tongue, antipyretic, sore throat and gum infections [05]. There are also others reports of the use of *Spilanthes acmella*, such as spices such as antiseptic, antibacterial, antifungal, antimalarial, remedy for toothache, influenza, cough and tuberculosis [06; 07].

In popular medicine, all parts of the plant are used (leaves, branches, inflorescences and fruits). Of these parts, infusions are made for the treatment of maladies of the mouth and throat, tuberculosis, pulmonary lithiasis, appetite stimulant, dyspepsia, malaria, antigripal, antispasmodic, antiasmatic, antianemic, antiscorbutic, among others. The main biological effects observed are: local anesthetic activity, flavoring, insecticide and bactericide whose effects are attributed to spilanthol or affinin, an isobutylamide present in the jambu [07]. Spilanthol is a secondary metabolite responsible for different types of biological activities, such as antioxidant, antimicrobial, cytotoxic and anti-inflammatory bioactivities [08].

Inflammation is a non-specific local reaction that occurs in the tissues that have suffered aggression. It is characterized by a series of alterations that aim to limit the aggressive effects to the organism, and for a long time it was considered as a disease, however, in the eighteenth century it was considered as a beneficial response of the organism, characterized by four typical signs: pain, redness, heat and edema, which may result in loss of function [09].

Although several compounds of *Spilanthes acmella* have been identified, compounds that contribute to its anti-inflammatory effect and the mechanisms by which they act rarely have been addressed [07]. Thus, the objective of this study was to systematically seek scientific evidence of the anti-inflammatory effect of *Spilanthes acmella* in *in vivo* and *in vitro* studies.

## Materials and Methods

This systematic review of the literature was performed in August 2017 from the construction of (PICO), where P = Question: What is the anti-inflammatory effect of *Spilanthes acmella* species; I: intervention: use of the species in *in vitro* and *in vivo* studies; C: control: allopathic anti-inflammatory and / or placebo; O: outcome: parameters that characterize inflammation.

### Search strategy

The online databases PubMed, Science Direct, Scopus, Springer and Clinikal Key were searched, without date restriction. The following keywords have been used for this period: *Spilanthes acmella*, anti-inflammatory effect, anti-inflammatory action. The review was expanded through manual search through Scholar Google, examining the articles found through the analysis of titles and abstracts. Only papers published in scientific journals were selected. In all databases, the search for eligible studies was carried out until October 2017, carried out by two independent researchers. Studies not yet published have not been included. The results found were arranged and tabulated using the Microsoft Excel program, then their respective titles, abstracts and source address was copied into document through the Microsof Word program for sorting.

### Screening and Selection

Both researchers listed titles and abstracts of eligible articles, if eligibility criteria were present in the title or abstract, the article was selected for full reading, or, if none of the criteria were met, the article was then removed from the prior selection. No blinding was done for the names of the authors, the institution they belonged to or the journal in which the publication appeared. Manual research was also carried out, where articles of good relevance for inclusion in the systematic review were found. Possible differences were resolved by a third researcher.

### Data Abstraction

All articles approved by the inclusion criteria were processed for extraction of the data. The information extracted included: author, year of publication, type of study, type of extract, dose administered, standard drug (s) used for control, time of observation and / or treatment, route of administration of the extract and protocol of effect observation.

**Eligibility Criteria**

*Inclusion criteria*: To be a study involving the use of the species *Spilanthes acmella*, studies that addressed action and the anti-inflammatory effect.

*Exclusion criteria*: Articles that did not present the inclusion criteria and the duplicates, articles with literature reviews and consensuses.

**Results and Discussion**

Eighty-two publications were found after an analysis of the abstracts was selected 73. After an analysis of the methods and results of these studies, four were eligible for inclusion in this systematic review, according to the flowchart below:

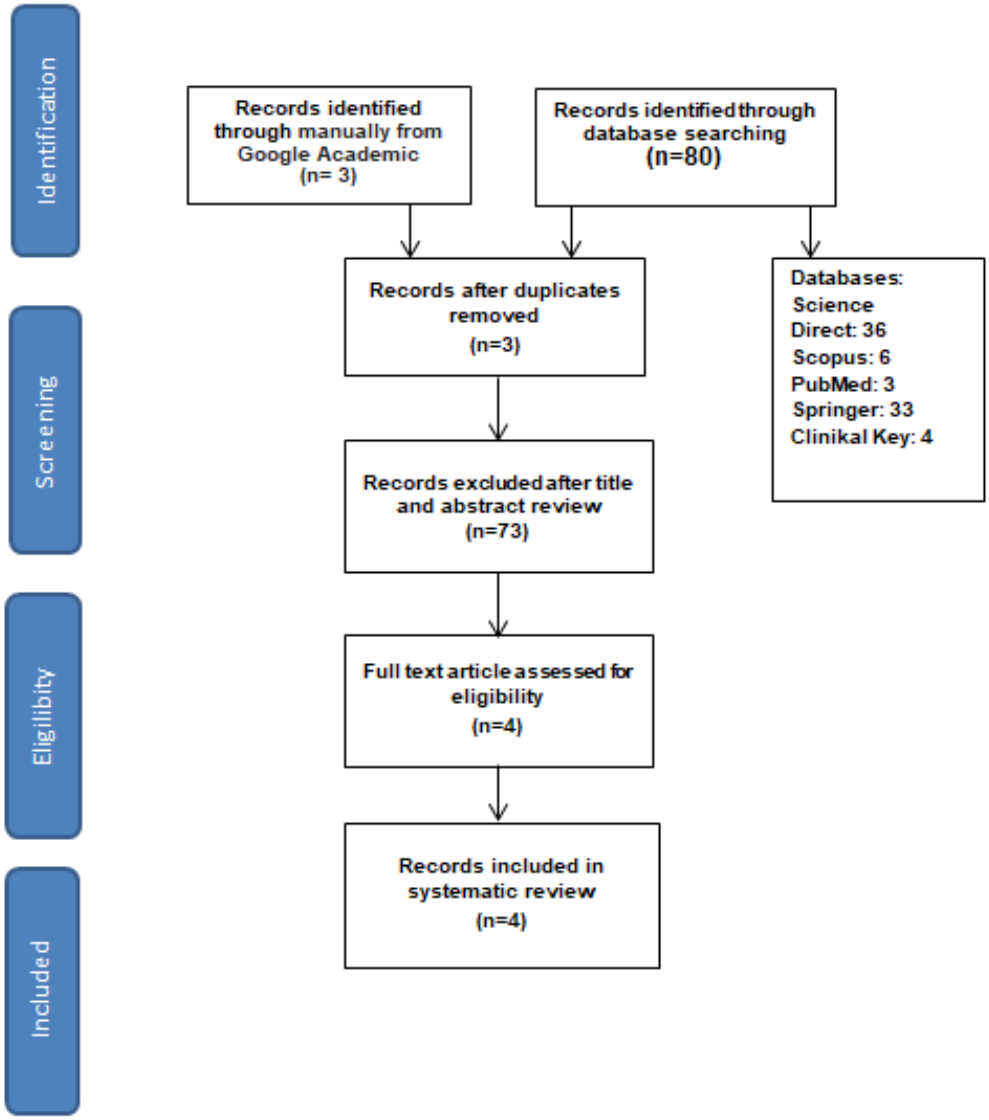


*Figure 1: Flow diagram of literature search and study selection*

From the four studies included in this systematic review, three of them were *in vivo* experiments using mice whose inflammation was obtained with the use of introduced carrageenan in the paw and the decrease in edema was measured by plethysmometry [10; 11; 12]. The fourth study was done *in vitro* experiment using murine macrophages. The description of the extracted data is shown in table 1.

| ARTICLE | AUTHOR | YEAR | DOSE | TYPE OF EXTRACT | MEDICATION PATTERN | PARAMETERS EVALUATED | TYPE OF STUDY | ROUTE OF ADMINISTRATION | METHODOLOGY | RESULTS |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Barman, S. | 2009 | 500 MG/kg p.o. | Etanolic Extract | Aspirin 100 MG/kg | • Plethysmometer<br>• Calculate percent inhibition | In vivo (rats) | Oral | Induction of paw edema with carrageenan 1% | Percent inhibition: Acute: 58.82% Subacute: 40.72% Chronic: 27.67% |
| 2 | Nitin Gupta | 2009 | | Methanólic Extract containing etosomes | Diclofenac Sodium Gel | • Plethysmometer<br>• Calculate percent inhibition | In vivo (rats) | Topic | Induction of paw edema with carrageenan 1% | 52.75% inhibition and close to allopathic drugs |
| 3 | A. Chakraborty | 2003 | 100, 200 and 400 mg / kg every 3 hours | Aqueous extract | Aspirin 100 MG/kg | • Plethysmometer<br>• Calculate percent inhibition | In vivo (rats) | Oral | Induction of paw edema with carrageenan 1% | It showed 52.6, 54.4 and 56.1% inhibition of paw edema, respectively, at the end of three hours |
| 4 | Li-Chen Wu | 2008 | 80µg/ml | Chloroform Extract | ---------- | • LPS, NO, COX-2, pro-inflammatory cytokines. | In vitro | | Induction by LPS in RAW 264.7 murine macrophages | Extracts of hexane and chloroform exhibited cytotoxic effects and strongly suppressed NO at 28% and 15%, respectively. |

The authors Barman [10] and Chakraborty [12] also included, in their studies, tests for analgesic action of the *Spilanthes acmella* extract in an experimental Swuiss mouse model. Both authors used aerial parts of the plant (leaves) while [11] used flowers to produce a gel with spilanthol to test the anti-inflammatory action topically. These authors included, in the study, *in vitro* test for antibacterial activity against *Escherichia coli*, mutants of *Streptococcus*, *Bacillus cereus* and *Lactobacillus aureus*. They demonstrated that the 5% concentration of *Spilanthes acmella* extract for antimicrobial action against the four types of microorganisms involved in oral infections shows pronounced antimicrobial action, comparable to the modern standard drug (moxifloxacin).

*Spilanthes acmella* refers to an important medicinal plant distributed in tropical and subtropical regions around the world, source of therapeutic and medicinal components. The main constituents are "spilanthol" and "acmellonate", which are often used to reduce toothaches and may induce saliva secretion [14; 07]. Once the physiological mechanisms of the inflammatory response have been recognized, research involving conventional or complementary therapeutic interventions is necessary and of great importance in the use of drugs that produce specific anti-inflammatory effects, besides animal models that allow control and comparison [15]. Thus, this study identified three studies that tested the anti-inflammatory activity of *Spilanthes acmella* in an animal model. Barman [10] presented in their results an anti-inflammatory activity of *Spilanthes acmella* extract against acute, subacute and chronic oral inflammation in the test group smaller than the control group that used aspirin. Similar results were also found for central and peripheral analgesia activity. The authors recognized that *Spilanthes acmella* has significant anti-inflammatory and analgesic activities. However, they have recommended additional studies in other models and clinical trials to confirm the results and to establish the mechanism of action of the exact and active principles involved in the anti-inflammatory and analgesic activity. Likewise, [2] demonstrated that in the acute inflammation model, the aqueous extract of *Spilanthes acmella* at doses of 100, 200 and 400 mg / kg orally produced dose-dependent inhibition of paw edema, but less than the drug standard, aspirin. The results of the study also suggested, according to the authors, that the aqueous solution of *Spilanthes acmella* demonstrated significant analgesic activity in acetic acid-induced models where the extract tested appeared to predominantly inhibit the peripheral pain mechanism.

Throughout the study identified in the systematic review [11] tested the anti-inflammatory action of *Spilanthes acmella* administered topically. For this, the authors obtained spilanthol which was purified by successive washes with acetone. The yield of purified spilanthol crystal was 407 mg / kg of 90% dry powder which was added to carbopol for gel production. The authors concluded that *Spilanthes acmella* is rich in various phyto-constituents and

that spilanthol is responsible for an anti-inflammatory and antibacterial activity and can be used as a biomarker creating new opportunities in modern pharmacological products for the treatment of inflammatory and microbial conditions.

Although the results of the study by [11] demonstrated a significant reduction in paw volume observed when compared to diclofenac standard gel. The percentage of inhibition was compared with the standard formulation, *i.e.* diclofenac sodium gel. Of the four studies included, the only *in vitro* test was that of [16] in which spilanthol was biopherically-guided isolated in murine macrophage. According to the authors, the analytical results revealed that spilanthol, isolated from chloroform extracts, efficiently regulated the production of inflammatory mediators IL-1β, IL-6 and TNF-α and attenuated expression of COX-2 and iNOS. Spilanthol demonstrated dose-dependent protection of macrophages activation with 60% and 20% of nitric oxide production at concentrations 90 and 360 μM, respectively.

These inhibitory properties were accompanied by a lower synthesis of nitric oxide and cyclooxygenase-2 mRNA and amount of protein, as well as lower production of cytokines by macrophages and lower activation of NF-kB in the nucleus [16]. Although *in vivo* studies of the quantitative evaluation of the reduction of paw edema through plethysmometry are not sufficient to be compared using different methodologies [10] and [12] in relation to the extract dose [10] used a dose of 500 mg / kg based on no oral acute toxicity test following guidelines from the Guidelines for the Testing of Chemicals (OECD) while [12] also based on acute toxicity test tested as doses of 100, 200 and 400 mg / kg. What is observed is the response in relation to decreasing the edema does not differ between doses tested. The studies included in this systematic review have shown that *in vitro* testing using spilanthol isolated from *Spilanthes acmella* species are more promising to investigate an anti-inflammatory action of this species than *in vivo* tests using crude extracts. Still, it is not necessary to overlook an importance of *in vivo* tests, since, as physiological interactions involving no living organism.

## Conclusion

Although studies investigating the anti-inflammatory effect of *Spilanthes acmella* are scarce, it is necessary to recognize the biological potential of this species. Regions located in the north of the country traditionally use jambu in cooking, scientific literature records its activity in several diseases, including stimulating the registration of innumerable patents related to the species or its most active component, spilanthol. We thus recognize the need for studies with adequate design whether *in vivo* or *in vitro* so that the population can use jambu either dermal or orally to treat inflammation effectively and safely.

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