Medicinal plants with mosquitoes repellent activity: a systematic review

Plantas medicinais com atividade repelente de mosquitos: uma revisão sistemática

Plantas medicinales con actividad repelente de mosquitos: una revisión sistemática

Anderson Ribeiro dos Santos
ORCID: https://orcid.org/0000-0003-3868-3380
Federal University of Sergipe, Brazil
E-mail: andersonfarmacia@yahoo.com.br
Alexia Mota Santos
ORCID: https://orcid.org/0000-0003-2715-6745
Federal University of Sergipe, Brazil
E-mail: alexiamotafarm@gmail.com
Fernando Henrique Oliveira de Almeida
ORCID: https://orcid.org/0000-0002-1728-9598
Federal University of Sergipe, Brazil
E-mail: fernandoalmeidafitofarm@gmail.com
Vinícius Freitas Arcieri de Medeiros
ORCID: https://orcid.org/0000-0003-0561-2420
Federal University of Sergipe, Brazil
E-mail: vfreitas12@gmail.com
Saulo Santos Matos
ORCID: https://orcid.org/0000-0002-6780-4236
Federal University of Sergipe, Brazil
E-mail: saulosm95@gmail.com
Thaís Feitoza de Carvalho
ORCID: https://orcid.org/0000-0001-7381-4791
Federal University of Sergipe, Brazil
E-mail: thaisfeitoza14@gmail.com
Carlos Adriano Santos Souza
ORCID: https://orcid.org/0000-0002-7913-2510
Federal University of Sergipe, Brazil
E-mail: carlos.953@gmail.com
Tamires Cardoso Lima
ORCID: https://orcid.org/0000-0001-6200-649X
Federal University of Sergipe, Brazil
E-mail: tamires.cl87@gmail.com
Francilene Amaral da Silva
ORCID: https://orcid.org/0000-0001-6729-2843
Federal University of Sergipe, Brazil
E-mail: farmsilva@hotmail.com

Abstract
Repellents are important allies in trying to prevent diseases transmitted by mosquito bites. Plants have been a source of various repellents and insecticides because they have a large reservoir of bioactive substances, in addition, their products have already been tested and are gaining space in research as a low-cost and easy-access alternative. A systematic review was carried out in the databases, Science Direct, Scielo, SciFinder, Springer, PubMed / Medline, Scopus and Web of Science, evaluated by three reviewers. Titles, abstracts and articles were analyzed in full in English, Spanish and Portuguese. To identify the articles, the following descriptors from the Medical Subject Headings (MeSH) were used: "insect repellents", "essential oils", "plants extract", "repellent activity", mosquitoes and plants. The bibliographic search resulted in 2274 records. Of these, 27 abstracts were considered potentially relevant, and at the end of the selection, 17 articles were included in their entirety. It was found that medicinal plants showed repellent activity against various species of mosquitoes, however due to the little standardization of the methodologies used and the products obtained it is necessary to develop standardized methods to guarantee the quality and reproducibility of clinical trials with medicinal plants.
Keywords: Medicinal plants; Essential oils; Mosquitoes; Repellent activity; Standardization; Aedes aegypti.

Resumo
Os repelentes são aliados importantes na tentativa de prevenir doenças transmitidas por picadas de mosquitos. As plantas têm sido fonte de diversos repelentes e inseticidas por apresentarem um grande reservatório de substâncias

bioativas, além disso, seus produtos já foram testados e vêm ganhando espaço em pesquisas como alternativa de baixo custo e fácil acesso. Foi realizada revisão sistemática nas bases de dados Science Direct, Scielo, SciFinder, Springer, PubMed / Medline, Scopus e Web of Science, avaliadas por três revisores. Títulos, resumos e Artigos foram analisados na íntegra nos idiomas inglês, espanhol e português. Para a identificação dos artigos, foram utilizados os seguintes descritores do Medical Subject Headings (MeSH): "repelentes de insetos", "óleos essenciais", "extrato de plantas", "atividade repelente", mosquitos e plantas. A busca bibliográfica resultou em 2274 registros. Destes, 27 resumos foram considerados potencialmente relevantes e, ao final da seleção, 17 artigos foram incluídos na íntegra. Verificou-se que as plantas medicinais apresentaram atividade repelente contra várias espécies de mosquitos, porém devido à pouca padronização das metodologias utilizadas e dos produtos obtidos é necessário o desenvolvimento de métodos padronizados que garantam a qualidade e reprodutibilidade dos ensaios clínicos com plantas medicinais.
Palavras-chave: Plantas medicinais, Óleos essenciais; Mosquitos; Atividade repelente; Padronização; Aedes aegypti.

Resumen
Los repelentes son aliados importantes para tratar de prevenir enfermedades transmitidas por picaduras de mosquitos. Las plantas han sido fuente de diversos repelentes e insecticidas porque cuentan con un gran reservorio de sustancias bioactivas, además, sus productos ya han sido probados y están ganando espacio en la investigación como alternativa de bajo costo y fácil acceso. Se realizó una revisión sistemática en las bases de datos Science Direct, Scielo, SciFinder, Springer, PubMed / Medline, Scopus y Web of Science, evaluadas por tres revisores. Los títulos, resúmenes y artículos fueron analizados íntegramente en inglés, español y portugués. Para identificar los artículos se utilizaron los siguientes descriptores de Medical Subject Headings (MeSH): "repelentes de insectos", "aceites esenciales", "extracto vegetal", "actividad repelente", mosquitos y plantas. La búsqueda bibliográfica dio como resultado 2274 registros. De estos, 27 resúmenes se consideraron potencialmente relevantes y, al final de la selección, se incluyeron 17 artículos completos. Se encontró que las plantas medicinales mostraron actividad repelente contra varias especies de mosquitos, pero debido a la falta de estandarización de las metodologías utilizadas y los productos obtenidos, es necesario desarrollar métodos estandarizados para asegurar la calidad y reproducibilidad de los ensayos clínicos con plantas medicinales.
Palabras clave: Plantas medicinales; Aceites esenciales; Mosquitos; Actividad repelente; Estandarización; Aedes aegypti.

1. Introduction

Mosquitoes are considered a serious public health problem due to serving as vectors for many important pathological conditions as well as inflicting significant discomfort through bites (Rueda, 2008; Ali et al., 2012). There are approximately 3500 mosquito species throughout the world, the majority of which are found in tropical and subtropical regions. However, only 10% have medical and veterinary relevance (Reiter, 2001). The most prevalent mosquitoes that act as vectors of human diseases are Aedes (Chikungunya, Zika, Dengue, and Yellow fever), Anopheles (malaria and filariasis), and Culex (Japanese encephalitis, West Nile virus, and filariasis) (Ghosh et al., 2012; Naseem et al., 2016). Recently, the Zika virus is creating damage in several parts of the world, including Brazil, Africa, Pacific Island, and Southeast Asia. According to Pan American Health Organization (PAHO), more than 40 countries or territories in the Americas recorded an epidemic of Zika virus in 2015-2016, with over 500,000 Zika suspected and confirmed cases (WHO, 2016).

Current and past strategies for mosquito control are based on synthetic insecticides, such as dichlorodiphenyltrichloroethane (DDT), temephos, and malathion. Although chemical agents have been successfully utilized in mosquitoes control during the last decades, the continuous use of these agents has resulted in the development of resistance, environmental impacts, and undesirable effects on non-target organisms, including humans (Deletre et al., 2019). All these factors have created a need for new biodegradable and renewable alternative insecticides. In this context, the use of plant-derived natural products for vector control has various attractive characteristics, including biodegradability, availability at affordable prices, smaller toxicity, and broad-spectrum target-specific activities against different mosquito species (Ghosh et al., 2012; Varun et al., 2013; Wilke & Marrelli, 2015).

Essential oils, also known as essences, volatile oils, or etheric oils, are defined as complex mixtures of several volatile and lipophilic compounds, being constituted principally by terpenes (mono and sesquiterpenes) and phenylpropanoids

(Guenther, 1972; Sangwan et al., 2001). A great number of essential oils extracted from different aromatic plants has shown great potential for pest management, since these oils possess high repellency against several arthropod species (Geetha & Roy, 2014). As an example, we can highlight the citronella (Cymbopogon nardus) essential oil, one of the most common essential oils in mosquito repellent patents (Pohlit et al., 2011). In the United States, the U.S. Environmental Agency (U.S. EPA), responsible for repellent products regulation, has recognized and registered citronella oil as an insect repellent ingredient for human applications since 1948 (EPA, 1999). Given the above, we present here a systematic review of clinical articles on medicinal plants with mosquito repellent activity.

2. Methodology

Protocol of this study was registered in the International Prospective Register of Systematic Reviews (PROSPERO), an open access database of systematic reviews administered at the Centre of Reviews and Dissemination, University of York, UK PROSPERO under number CRD42017070923 (BOOTH et al., 2012).

Article search strategy

The search strategy was carried out based on studies available in scientific literature until August 2021. There was no initial time limit. The bibliographic literature search was conducted in different scientific databases, including Science Direct, Scielo, SciFinder, Springer, PubMed/Medline, Scopus, and Web of Science. In addition, a manual search was performed by analyzing the references of the included articles. The literature search was performed in English, Spanish and Portuguese. For identification of articles, the following descriptors of the Medical Subject Headings (MeSH) were used: "insect repellents", "essential oils", "plants extract", "repellent activity", "mosquitoes" and "plants". The descriptors were adapted to each database and combined through the Boolean operators (OR, AND, and NOT).

The titles and abstracts were evaluated according to predefined inclusion criteria to determine the relevance of this topic: clinical trials evaluating the use of medicinal plants as mosquito repellents; clinical trials with medicinal plant essential oils and clinical trials with plant products. The exclusion criteria were comments, editorials, articles not published in Portuguese, Spanish, and English, and articles not available in full.

Initially, the records were exported to Mendeley program 1.16.3 ©. Data extraction and initial assessment of the relevant records followed by the abstracts and full text was conducted by two independent reviewers (ARS and AMS). Then, selection divergences were resolved by a third reviewer (CASS) and consensus-building. After a consensus meeting, articles that were not within the scope of this review were excluded. Cohen's Kappa statistic was used to measure reliability among the evaluators (Mchugh, 2012).

Evaluation of repellent activity and repellent product quality

To evaluate interventions with medicinal plants, the following criteria were used: randomization, blinding of the participants (double-blind), description of the methods of randomization, and report of losses and exclusions after randomization. The used features to evaluate the quality of the products tested in the clinical trials were: characteristics of the medicinal plant; botanical identification; plant parts; type of product (fresh, dry, or extracts) and standardization of products (dose of active constituents / biomarkers) (Gagnier et al., 2006).

Quality of clinical trials of repellent activity with medicinal plants

This evaluation was performed according to the Main Items for Reporting Systematic Reviews and Meta-analyzes

(PRISMA). This statement provides essential information on the methodology and development of systematic reviews, as follows: terminology, research question formulation, study identification and data mining, study quality and results of publication (Moher et al., 2009).

3. Results

Initially, 2,274 records were found in the databases used. Of these, 27 abstracts were considered potentially relevant and, at the end of the selection, 17 articles were included in this systematic review according to the adopted inclusion and exclusion criteria (Figure 1). Most studies came from India 23% (n = 4), followed by Thailand 17% (n = 3), Colombia, Johannesburg, Ethiopia, Nigeria, Nepal, Malaysia, Bolivia, Benin, USA, Guatemala, and Peru.

Regarding the design of clinical trials, 71% (n = 12) were not randomized and 29% (n = 5) were randomized Table 1. The control groups present in the research were volunteers who did not apply any odorous or repellent substance on the arm. The mean duration of the study was $(\mu) = 1.3$ months with a standard deviation of $(\sigma) = 0.9$ Table 2.

As for the methodology of clinical trials, the main negative points were the lack of randomization, blinding of the participants, and no description of losses and exclusions Table 1. The main products used were essential oil with 59% (n = 10), followed by crude extract with 29% (n = 5) Table 3. The study included eighteen species of vectors, with an emphasis on the species Aedes aegypti, which was present in 28% of the analyzed studies Table 1.

The leaf was the main part of the plant used, 47% (n=8) in the preparations of repellents and the most used pharmaceutical form was a solution present in 47% (n=8) of the studies. Among the 17 studies, only two standardized their products according to the substance/markers present Table 3. Furthermore, only 6% (n = 1) of the studies reported not having achieved significant findings, while 94% (n = 16) of the studies speculated positive repercussions regarding the efficacy of the medicinal plant tested.

Concerning the technological quality of clinical trials involving medicinal plants with repellent activity, the main absences verified were: characterization of the medicinal plant (64.70%), standardization of products (94.11%), concentration of used extraction solvent (52, 94%), and qualitative and purity tests (100%) Table 3.

Figure 1 – Flowchart of the Selection Process of Included Studies.
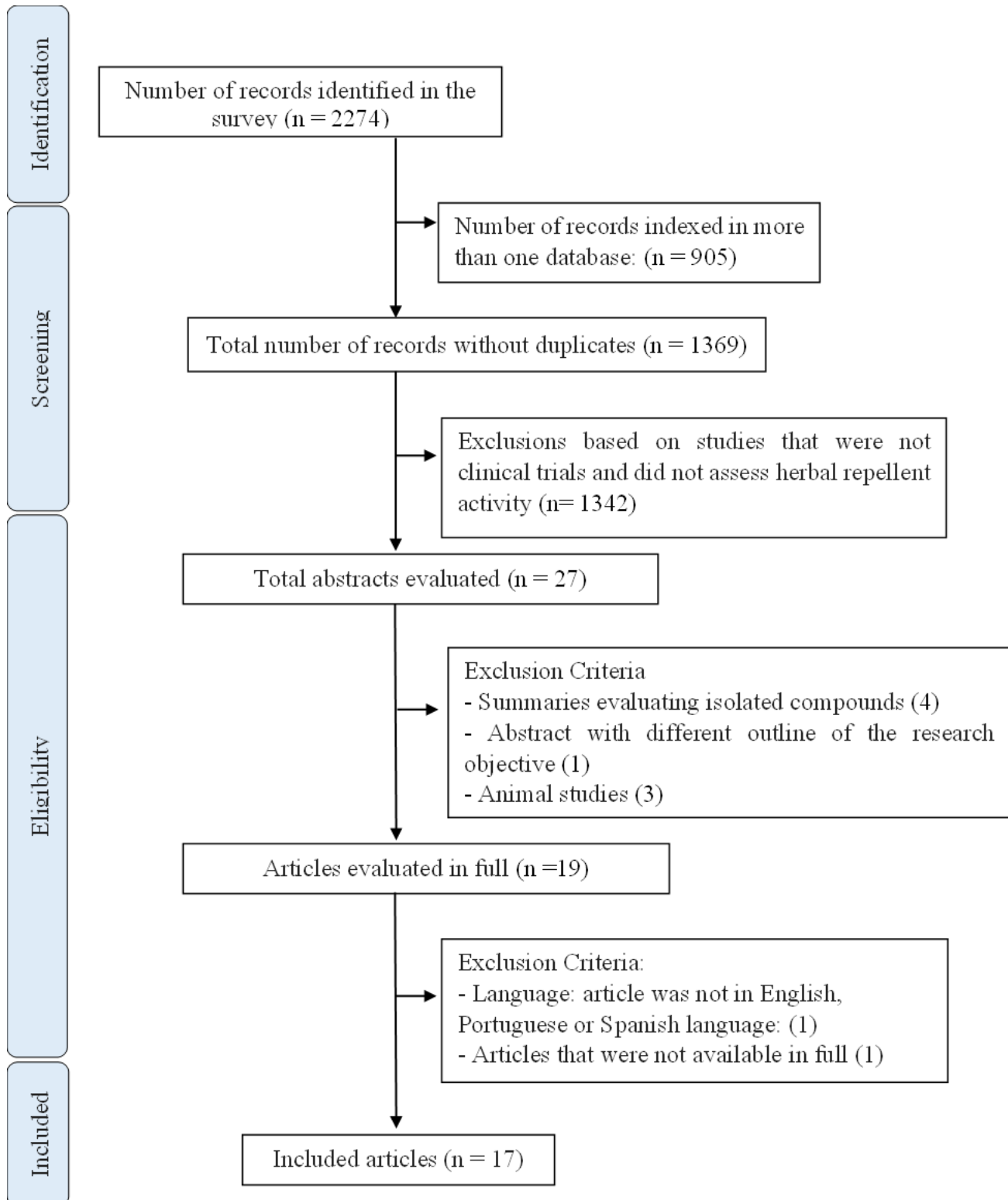
Source: Own Authorship.

Table 1. Evaluation of the clinical trials methodology (randomization, blinding, description of losses and exclusions).

Author's name, year and research country	Repellence time (minutes)	Mosquito vector	Positive points	Negative points
Hill, Lenglet, Arnez, & Carneiro, 2007, Bolivia	Not described	*Plasmodium falciparum* and *P. vivax*	Randomization, description of randomization methods, blinding, treatment group, and control group (placebo)	No description of losses and exclusions
Abagli, Alavo, Avlessi, & Moudachirou, 2012, Benin	180-360 min	*Anopheles gambiae; Aedes* sp. and *Culex quinquefasciatus*	Treatment group and control group	No description of losses and exclusions, no blinding and no randomization
Sritabutra & Soonwera, 2013, Thailand	54 and 96 min*	*Aedes aegypti* and *Culex quinquefasciatus*	Treatment group and positive and negative control groups	No description of losses and exclusions, no blinding and no randomization
Elango et al., 2010, India	30-150 min	*Culex tritaeniorhynchus*	Treatment group and control group	No description of losses and exclusions, no blinding and no randomization
Santamaría, Cabrera, Zipa, & Pardo, 2012, Colombia	240-338,2 min	*Culicoides pachymerus*	Treatment group and control group	No description of losses and exclusions, no blinding and no randomization
Govere, Durrheim, Baker, Hunt, & Coetzee, 2000, Johannesburg	180-360 min	*Anopheles arabiensis*	Treatment group and control group	No description of losses and exclusions, no blinding and no randomization
Govindarajan & Sivakumar, 2012, India	100 min	*Culex quinquefasciatus* and *Aedes aegypti*	Treatment group and control group	No description of losses and exclusions, no blinding and no randomization
Hadis, Lulu, Mekonnen, & Asfaw, 2003, Ethiopia	Not described	*Mansonia uniformis, M. nigerrima, M. fricana, Anopheles pharoensis, A. tenebrosus* and *Taeniorhnyrchus cristatus.*	Randomization, and treatment group and control group	No description of losses and exclusions, and no blinding
Murugan et al., 2012, India	120-180 min	*Anopheles stephensi, Aedes aegypti* and *Culex quinquefasciatus*	Treatment group and control group	No description of losses and exclusions, no blinding and no randomization
Karunamoorthi, Ilango, & Murugan, 2010, India	192,6-390,6 min	*Anopheles arabiensis*	Treatment group and control group	No description of losses and exclusions, no blinding and no randomization
Keziah, Nukenine, Danga, Younoussa, & Esimone, 2015, Nigeria	60-180 min	*Aedes aegypti*	Treatment group and control group	No description of losses and exclusions, no blinding and no randomization
Soonwera & Phasomkusolsil, 2015, Thailand	60-126,7 min	*Aedes aegypti* and *Culex quinquefasciatus*	Treatment group and control group	No blinding and no randomization
Sajo et al., 2015, Nepal	Not described	Not described	Randomization, and treatment group and control group	No description of losses and exclusions, and no blinding
Misni, Sulaiman, Othman, & Omar, 2009, Malaysia	120 min	*Aedes albopictus*	Treatment group and positive and negative control groups	No description of losses and exclusions, no blinding and no randomization
Moore, Darling, Sihuincha, Padilla, & Devine, 2007, Guatemala and Peru	300 min	*Anopheles darlingi*	Randomization, description of randomization methods, blinding, treatment group, control group, and description of losses and exclusions	-
Rajan, Hein, Porte, & Wikel, 2005, EUA	Not described	*Aedes aegypti*	Randomization, description of randomization methods, blinding, treatment group, control group, and description of losses and exclusions	-
Choochote et al, 2007, Thailand	30-150 min	*Aedes aegypti*	Treatment group and control group	No blinding and no randomization

*Ae. Aegypti. Source: Own Authorship.

Table 2. General characteristics of the studies included in the systematic review.

Author's name, year and research country	Study duration	Research limitations
Hill, Lenglet, Arnez, & Carneiro, 2007, Bolivia	7 months	Not described
Abagli, Alavo, Avlessi, & Moudachirou, 2012, Benin	4 months	Not described
Sritabutra & Soonwera, 2013, Thailand	Not described	Not described
Elango et al., 2010, India	Not described	Not described
Santamaría, Cabrera, Zipa, & Pardo, 2012, Colombia	2 months	Not described
Govere, Durrheim, Baker, Hunt, & Coetzee, 2000, Johannesburg	Not described	Not described
Govindarajan & Sivakumar, 2012, India	Not described	Not described
Hadis, Lulu, Mekonnen, & Asfaw, 2003, Ethiopia	1 month	Variation in mosquito species and different methods for obtaining essential oils
Murugan et al., 2012, India	Not described	Not described
Karunamoorthi, Ilango, & Murugan, 2010, India	Not described	Not described
Keziah, Nukenine, Danga, Younoussa, & Esimone, 2015, Nigeria	3 weeks	Not described
Soonwera & Phasomkusolsil, 2015, Thailand	Not described	Not described
Sajo et al., 2015, Nepal	6 days	Not described
Misni, Sulaiman, Othman, & Omar, 2009, Malaysia	Not described	Different mosquito species and not standardized testing protocols
Moore, Darling, Sihuincha, Padilla, & Devine, 2007, Guatemala and Peru	34 days	Not described
Rajan, Hein, Porte, & Wikel, 2005, EUA	Not described	Not described
Choochote et al, 2007, Thailand	Not described	Not described

Source: Own Authorship.

Table 3. Standardization of the herbal medicinal products evaluated in this systematic review.

Author's name, year, research country	Species	Vegetable drug	Herbal product	Standardization	Pharmaceutical form
Hill, Lenglet, Arnez, & Carneiro, 2007, Bolivia	*Eucalyptus maculata citriodon*	Not described	Essential oil	*p*-mentan-3,8-diol (PMD) 30%	Not described
Abagli, Alavo, Avlessi, & Moudachirou, 2012, Benin	*Hyptis suaveolens*	Leaves	Essential oil	Not described	Solution
Sritabutra & Soonwera, 2013, Thailand	*Cymbopogon nardus**	Aerial parts	Essential oil	Not described	Solution
Elango et al., 2010, India	*Cocculus hirsutus***	Leaves	Crude extract	Not described	Suspension
Santamaría, Cabrera, Zipa, & Pardo, 2012, Colombia	*Corymbia citriodora* and *Cymbopogon citratus*	Leaves	Essential oil	Not described	Not described
Govere, Durrheim, Baker, Hunt, & Coetzee, 2000, Johannesburg	*Eucalyptus maculata citrodon*	Not described	Not described	PMD 0.574/0.8 (*p/p*)	Lotion
Govindarajan & Sivakumar, 2012, India	*Eclipta alba* and *Andrographis paniculata*	Leaves	Crude extract	Not described	Solution
Hadis, Lulu, Mekonnen, & Asfaw, 2003, Ethiopia	*Ruta chalepensis****	Aerial parts	Essential oil	Not described	Solution
Murugan et al., 2012, India	*Citrus sinensis*	Aerial parts	Crude extract	Not described	Suspension
Karunamoorthi, Ilango, & Murugan, 2010, India	*Cymbopogon citratus*	Leaves	Crude extract	Not described	Not described
Keziah, Nukenine, Danga, Younoussa, & Esimone, 2015, Nigeria	*Ocimum gratissimum* L. and *Lantana camara*	Leaves	Crude extract	Not described	Cream
Soonwera & Phasomkusolsil, 2015, Thailand	*Cymbopogon citratus e Cananga odorata*	Aerial parts	Essential oil	Not described	Solution
Sajo et al., 2015, Nepal	*Cymbopogon winteratus*	Leaves	Essential oil	Not described	Not described
Misni, Sulaiman, Othman, & Omar, 2009, Malaysia	*Piper aduncum*	Leaves	Essential oil	Not described	Solution
Moore, Darling, Sihuincha, Padilla, & Devine, 2007, Guatemala and Peru	*Corymbia citriodora* and *Cymbopogon citratus*	Not described	Essential oil	Not described	Solution
Rajan, Hein, Porte, & Wikel, 2005, EUA	*Allium sativum*	Bulb	Not described	Not described	Capsule
Choochote et al, 2007, Thailand	*Curcuma zedoaria* Roscoe****	Aerial parts	Essential oil	Not described	Solution

**C. odorata* Hook., *Syzygium aromaticum, Z. officinale* Roscoe, *Cymbopogon citratus, Cymbopogon nardus, Eucalyptus citriodara* Hook, *Citrus reticulata,* and *Ocimum basilicum.*
***Aegle marmelos, Andrographis lineate, Andrographis paniculata, Eclipta prostrata,* and *Tagetes erecta*
*** *Azidirachta indica, Chrysanthemum cineraraiefolium, Ruta chalepensis,* and *Eucalyptus maculata citriodora*
**** *Amomum xanthioides, Curcuma zedoaria* Roscoe, *Kaempferia galanga* L, *Anethum graveolens* L, *Apium graveolens* L., *Carum carvi* L, *Foeniculum vulgare, Piper longum* L, *Zanthoxylum limonella* and *Zanthoxylum piperitum* (L.) DC. Source**:** Own Authorship.

4. Discussion

According to the World Health Organization, vector-borne diseases account for more than 17% of all infectious diseases, causing more than 700,000 deaths annually. Diseases such as malaria, dengue, schistosomiasis, African human trypanosomiasis, leishmaniasis, Chagas disease, yellow fever, Japanese encephalitis, and onchocerciasis are among the main vector-borne diseases (WHO, 2020).

Due to the burden of these diseases, chronic suffering, disability, and morbidity throughout life, the WHO elaborated the "Global Vector Control Response (GVCR) 2017–2030", which provides strategic guidance for urgent strengthening of vector control to prevent disease and respond to outbreaks. Among the recommendations are the development and evaluation

of new tools, technologies, and approaches for vector-borne diseases, including disease control and management technologies (WHO, 2017).

In this context, the field of study of medicinal plants as repellents is important, since repellents must be safe, agreeable, and ecologically sustainable. Moreover, the cost of the production of repellents is another significant factor that corroborates to the development of research on flora.

Discussion of Articles found in the search

Essential Oils (EO) are complex mixtures of volatile organic compounds such as terpenes, sesquiterpenes, alcohols, esters, aldehydes, ketones, lactones, phenols, and phenol eters (Guenther, 1972; Nerio et al., 2010). In this review, most studies were performed with plants rich in essential oils. The studies of Choochote et al. (2007), Hadis et al., (2003); Sritabutra and Soonwera (2013), evaluated the efficacy of essential oils in more than one medicinal plant species.

Hadis et al. (2003) evaluated the repellent activity of essential oils of Eucalyptus maculata citriodon, Ruta chalepensis, Chrysanthemum cinerariaefolium, and Azadiracta indica. In this study, all medicinal plants showed repellent activity at different concentrations (40%, 50%, and 75%). A possible explanation could be due to the variation of species in the mosquito population during the tests at different concentrations. The variation of species composition during the tests, may have affected the result of increasing protection by increasing or decreasing the number of sensitive or tolerant species of mosquitoes. Eucalyptus maculata citriodon oil gave a protection equivalent to that of N -diethyl-m-toluamide (DEET) in identical concentrations. This result is important given the increased resistance to this repellent, caused by mutations in the vectors. DEET is the most common ingredient in mosquito repellents which is considered to act by inhibiting acetylcholinesterase in mosquitoes. Stanczyk et al. (2010) identified females of Aedes aegypti insensitive to DEET as a result of a genetically altered dominant trait.

Choochote et al. (2007) evaluated ten essential oils extracted from medicinal plants, however, only Zanthoxylum piperitum, Anethum graveolens, and Kaempferia galanga exercised protection against A. aegypti, with an average complete protection time of 1h, 0.5h, and 0.25 h, respectively. The highest potential was established from Z. piperitum oil + 10% vanillin (2.5 h, range = 1–2.5 h). This was probably due to the lower rate of evaporation and the greater persistence in the skin of vegetable products after the addition of vanillin. According to Raveau et al. (2020), the volatile nature and instability of the EOs components are the primary causes of EOs degradation.

Sritabutra e Soonwera (2013) evaluated the repellency effect of several herbal oils against medically important mosquitoes. The results demonstrated that clove oil, citronella oil, and lemongrass oil had high potency to control Aedes aegypt, and Culex quinquefasciatus. The phytochemical constituent of clove and citronella oil such as eugenol, citronellol, geraniol, citral, and limonen has pharmacological properties for mosquito repellent activity (Kang et al., 2009; Maia & Moore, 2011; Shapiro, 2012). Despite the positive results, the oil repellency when compared to the positive control (KorYor 15®) exhibited a shorter repellency time.

Studies by Hill et al. (2007), Misni et al. (2009), Abagli et al. (2012), Sajo et al. (2015), evaluated the species Eucalyptus maculata citriodon, Hyptis suaveolens, Cymbopogon winteratus, Piper aduncum. All the EOs of the analyzed species presented repellence, presenting better results in higher concentrations. However, when compared to the positive control group, the EOs had a lower repellency time. Hill et al. (2007) study showed an equal time of repellency, only when associating the EO with the positive control group (N,N-Dietil-m-toluamida – DEET). The ingredient is recommended as the positive control (usually 20% in ethanol) against which the effectiveness of alternative mosquito repellents is judged (WHO, 2009).

Evaluation of repellent activity and quality of products used

Although studies have shown the effectiveness of herbal repellent products, when applied to the skin, the protection provided usually dissipates rapidly (Trongtokit et al., 2005; Li et al., 2013;). In the case of essential oils, this fact is related to high volatility, a property that may be enhanced with the development of formulations that could be able to keep the principles active for an extended period. Considering the high volatility of EO, repellent performance is heavily dependent on the product's composition and capacity to prolong the duration of action. According to Oliveira et al, 2020, formulations based on creams, polymers, mixtures, or controlled-release microcapsules provide better results in repellency.

According to a study by Choocote et al. (2007) assessed in this review, a compound combined with essential oil that was demonstrated to increase repellency time was vanillin. Additionally, the repellency time of pure oil was shorter when compared with the mixture of 10% vanillin. Keziah et al., (2012) analyzed the formulation of crème with crude extract of leaves Ocimum gratissimum and Lantana camara L. which presented repellent activity against Aedes aegypti L., without exhibiting adverse reactions in the volunteers. Therefore, fixing additives and the production of repellents combined are possibilities that can increase the effectiveness and economic value of essential oils with repellent activity.

The process of transforming a plant into a medicine must adhere to established norms to ensure the plant's chemical and pharmacological integrity, ensuring consistent biological action and user safety. (Han et al.,2019). When analyzing the articles in this study, there are a significant number of limitations and absences, where most of the articles did not present the characteristics of medicinal plants in the tests and there was hardly any standardization of their products according to their chemical markers, there was also scarce descriptions of qualitative and quantitative quality control tests (only two articles presented). Such absences will interfere with the quality of the articles as well as question the safety and efficacy of the final product.

In the present study, only two articles, Hill et al. (2007) and Govere et al. (2000), described a standardization of the repellent product based on a biomarker. The substance used as a marker was p-mentan-3,8-diol (PMD), an essential oil classified as monoterpene and that can be extracted from aromatic plants such as eucalyptus (Corymbia citriodora) and has proven insect repellent properties similar to DEET (Carroll & Loye, 2006).
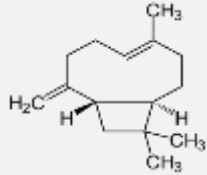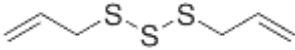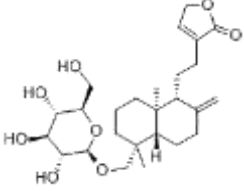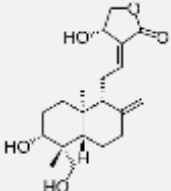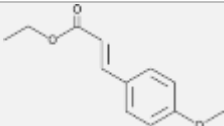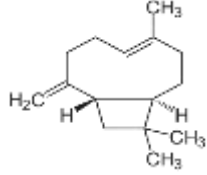
Despite the findings, there are some difficulties inherent to the development of the herbal product, due to the complexity of the plant's constituents,the raw material, and the variability in the quality of the products obtained from the same plant species. These characteristics are related to the factors and conditions of the place of cultivation, the procedure of collection, handling, and processing of the vegetable raw material. Thereby, plant products will show variations, further increasing the requirement for standardization to guarantee efficacy, safety, and quality (Liu et al., 2018).
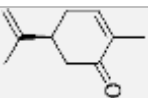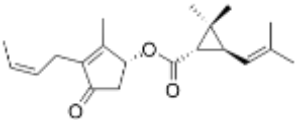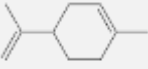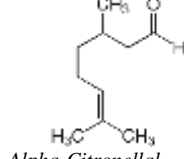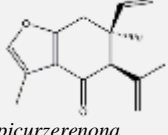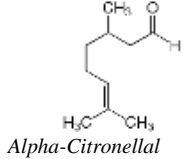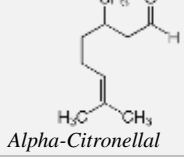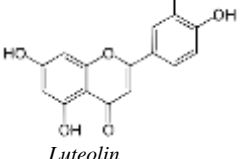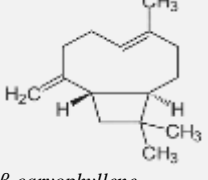
The standardization and quality control of herbal medicines is carried out based on the content of biomarker, which by definition is a substance or a group of them, which is present mainly in a certain plant species and is the responsible or one of those responsible for the plant's pharmacological activity. Additionally, biomarkers must be stable and capable of analysis by analytical and bioanalytical processes, must guarantee the results' reliability, and must be validated according to current legislation. Hence, the biomarker's presence in an appropriate quantity demonstrates that the other components will be equally represented allowing the reproducibility of new studies with the same plant. Therefore, biomarkers are indispensable requirements in the production of medicines, in the planning and monitoring of technological production, and for studies on the stability of intermediate and final products. Thus, standardization is a prerequisite for constant therapeutic effects and patient safety (Han et al., 2019; Liu et al., 2018).
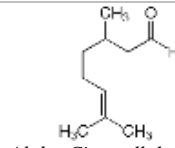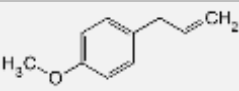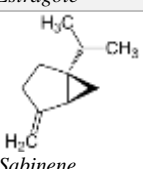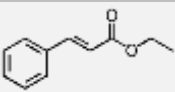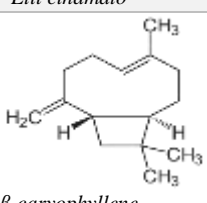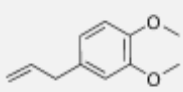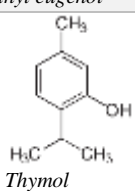
From this perspective of standardizing a product of plant origin, only two executable works are standardization and quality control tests of the obtained products, and most of these works may have carried out these tests. This statement can be
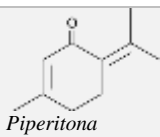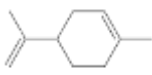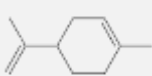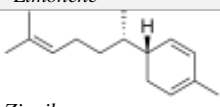
observed in Table 4, which presents findings in the literature on experiments for the identification and analysis of plant biomarkers that were used in the studies. Also in this table, the main compounds of the plants used in the studies are from the class of essential oils and the most used method was Gas Chromatography coupled with Mass Spectrometry (CG-MS). This fact is justified by the aromatic and low molecular weight which are characteristics of the main biomarkers present in the medicinal species analyzed (Adams, 2007).

Table 4 - Majority Compounds Described in the Literature of the Plants Selected for Review.

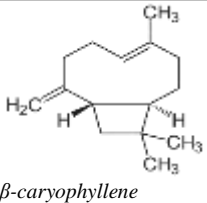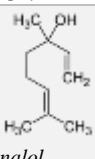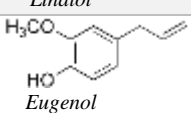| Species	Part of plant used	Biomarker	Method used to identify the marker substance	Reference
Aegle marmelos	Leaves	 *β-caryophyllene*	GC-MS	Pant *et al., 2019.*
Allium sativum	Clove	 *Diallyl trisulfide*	GC-MS	Satyal, Craft, Dosoky, & Setzer, 2017.
Amomum xanthioides	Fruits	 *Camphor*	GC-MS	Ao, Wang, Chen, Li, & Dai, 2019.
Andrographis lineate	Leaves	 *Neoandrographolide*	HPLC-MS	Dalawai, Aware, Jadhav, & Murthy, 2019.
Andrographis paniculata	Leaves	 *Andrographolide*	GC-MS	Edwin et al., 2016.
Anethum graveolens L	Aerial parts	 *Limonene*	GC-MS	Snuossi et al., 2016.
Azidirachta indica	Leaves	 *Ethyl-p-methoxycinnamate*	GC-MS	Umar et al., 2014.
Cananga odorata	Flowers	 *β-caryophyllene*	GC-MS	Qin et al., 2014.

Carum carvi L	Seeds	 *Carvone*	*GC*-MS	Laribi, Kouk, Mougou, & Marzouk, 2010.
Chrysanthemum cinerariaefolium	Flowers	 *Cinerin I*	HPLC-MS	Cappiello et al., 2012.
Citrus reticulata	Fruits	 *Limonene*	*GC*-MS	Tao, Jia, & Zhou, 2014.
Citrus sinensis	Fruits	 *Limonene*	*GC*-MS	Qiao et al., 2008.
Cocculus hirsutus	Whole plant	*Total flavonoids*	UV-VIS	Thavamani, Mathew, & Palaniswamy, 2014.
Corymbia citriodora	Leaves	 *Alpha-Citronellal*	*GC*-MS	Mohamed et al., 2019
Curcuma zedoaria Roscoe	Rhizome	 *Epicurzerenona*	*GC*-MS	Huang, 2020.
Cymbopogon nardus	Leaves	 *Alpha-Citronellal*	*GC*-MS	Da Silva et al., 2020.
Cymbopogon winteratus	Leaves	 *Alpha-Citronellal*	*GC*-MS	Silva et al., 2018.
Eclipta alba	Aerial parts	 *Luteolin*	UPLC-MS/MS	Sollepura Boregowda et al., 2019.
Eclipta prostrata	Leaves	 *β-caryophyllene*	*GC*-MS	Ogunbinu et al., 2009

Eucalyptus citriodara	Leaves	Alpha-Citronellal	GC-MS	Manh, Hue, Hieu, Tuyen, & Tuyet, 2020
Foeniculum vulgare	Leaves	Estragole	GC-MS	Marrelli et al., 2020.
Hyptis suaveolens	Leaves	Sabinene	GC-MS	Bayala et al., 2020.
Kaempferia galanga L	Rhizome	Etil cinamato	GC-MS	Liu et al., 2014.
Lantana câmara	Aerial parts	β-caryophyllene	GC-MS	Nea et al., 2020.
Ocimum basilicum.	Aerial parts	Methyl eugenol	GC-MS	Muráriková et al., 2017.
Ocimum gratissimum	Leaves	Thymol	GC-MS	Lima et al., 2018.
Piper aduncum	Aerial parts	Camphor	GC-MS	Monzote, Scull, Cos, & Setzer, 2017.
Piper longum L	Leaves	β-caryophyllene	GC-MS	Liu, Song, & Hu, 2007.
Ruta chalepensis	Aerial parts	Linalol	GC-MS	Jaradat et al., 2017.
Syzygium aromaticum	Clove dried	Eugenol	GC-MS	Radunz et al., 2019

Tagetes erecta	Leaves	*Piperitona*	*GC*-MS	Marques et al., 2011.
Zanthoxylum limonella	Fruits	*Limonene*	*GC*-MS	Itthipanichpong, Ruangrungsi, & Pattanaautsahakit, 2002.
Zanthoxylum piperitum	Fruits	*Limonene*	*GC*-MS	Choochote et al, 2007.
Zingiber officinale Roscoe	Rhizome	*Zingiberene*	*GC*-MS	Moon, Cho, & Kim, 2011.

*GC-MS - Gas Chromatography Coupled to the Mass Spectrometer; **HPLC-MS - High-Efficiency Liquid Chromatography Coupled with Mass Spectrometer; ***UPLC-MS/MS - Ultra Performance Liquid Chromatography Coupled with Tandem Mass Spectrometry; ****UV-VIS - Ultraviolet–Visible Spectrophotometry. Source: Own Authorship.

Evaluation of clinical trials of medicinal plants with repellent activity

Several methods were used to assess mosquito repellent activity by the studies that were included in this review, mostly amounts of EO or extracts were previously dissolved in a fixed volume of solvent and applied evenly to arms, legs, mosquito nets, or cages. To calculate the percentage of repellency, most studies evaluated the number of mosquito bites at certain times, the number of mosquitoes that landed and the time elapsed until the first bite on the arm or lower limbs.

Due to the variability in the methodologies found in the tests to assess repellency (different conditions, variables, and parameters), comparisons between the results of different clinical trials are not possible. Consequently, the results can only be compared with positive or negative control, in the same clinical trial, in order to classify the degree of repellency.

In this context, effective assessment is necessary following the adaptation of the CONSORT instrument (Table 5) for clinical trials with medicinal plants, since it allows the assessment of various aspects that interfere with the transparency of the study report with medicinal herbs. Many studies did not describe some methods (purity tests, biomarker standardization) and who performed them (e.g.name of the laboratory). Furthermore, they also failed to inform whether a product sample (eg, retention sample) was kept and, if so, where it was kept or deposited.

The standardized extracts were of high quality containing consistent levels of compounds, submitted to rigorous control. The analysis of the chemical profile is essential since using the appropriate techniques can provide a precise report of its constituents, besides providing qualitative and quantitative information (Folashade, Omoregie, & Ochogu, 2012). In view of the fact that the studies do not report the sample calculation and the size of the sample, these studies may be speculated to have small chances of being statistically significant (Sakpal, 2010).

The World Health Organization Guidelines for testing the efficacy of mosquito repellents for human skin (2009), recommends that the method of choice be performed in humans for producing results relevant to the conditions of use. In this review, the study by Hill et al., (2007), endorsed Eucalyptus maculata citriodon with p-menthane 3.8 diol (PMD), applied in mosquito nets making the evaluation of the product's repellency efficacy not possible.

Table 5. Evaluation of the clinical trials of medicinal plants according to recommendations from PRISMA (Main Items for Reporting Systematic Reviews and Meta-analyzes) statement.

Author's name, year and research country	Research limitations
Govere, Durrheim, Baker, Hunt, & Coetzee, 2000	Characteristics of the medicinal plant (botanical identity), concentration of extraction solvent used, standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Hadis, Lulu, Mekonnen, & Asfaw, 2003	Characteristics of the medicinal plant (botanical identity), concentration of extraction solvent used, standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Rajan, Hein, Porte, & Wikel, 2005	Characteristics of the medicinal plant (license in the country in which the study was conducted), standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Choochote et al., 2007	Description of the purity tests
Moore, Darling, Sihuincha, Padilla, & Devine, 2007	Description of the qualitative and purity tests
Hill, Lenglet, Arnez, & Carneiro, 2007	Characteristics of the medicinal plant (botanical identity), standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Misni, Sulaiman, Othman, & Omar, 2009	Standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Karunamoorthi, Ilango, & Murugan, 2010	Characteristics of the medicinal plant (botanical identity), standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Elango et al., 2010	Standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Murugan et al., 2012	Characteristics of the medicinal plant (botanical identity), standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Abagli, Alavo, Avlessi, & Moudachirou, 2012	Characteristics of the medicinal plant (botanical identity), standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Santamaría, Cabrera, Zipa, & Pardo, 2012	Characteristics of the medicinal plant (botanical identity), dosage regimen and standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Govindarajan & Sivakumar, 2012	standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Sritabutra & Soonwera, 2013	Characteristics of the medicinal plant (botanical identity), standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Keziah, Nukenine, Danga, Younoussa, & Esimone, 2015	Standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Soonwera & Phansomkusolsil, 2015	Characteristics of the medicinal plant (botanical identity), standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests
Sajo et al., 2013	Characteristics of the medicinal plant (botanical identity), concentration of extraction solvent used, standardization (quantity of active constituents/chemical marker per dosage unit form) of the herbal product, and description of the qualitative and purity tests

Source: Own Authorship.

5. Conclusion

Most studies included in this review were of medicinal plants rich in essential oils which demonstrated good repellent activity against several species of mosquitoes, however due to the high volatility of these compounds, the protection time is reduced when compared to positive control. Therefore, despite these products' potential, the development and standardization of products that increase the repellency time are required to improve mosquito repellent efficiency.

The absence of standardization of the methodologies was an obstacle to the evaluation of the articles included in this review. As a result, a standardized protocol capable of comprehensively evaluating the quality of clinical trials of medicinal plants with mosquito repellent activity is recommended. We hope that this review will contribute to future studies of medicinal plants with repellent activity, given the great necessity for new products to prevent diseases transmitted by mosquitoes.

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