LARA JARDIM COLLARES

SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS OF PHYTOCHEMICALS AS INSECTICIDES: TRENDS AND KNOWLEDGE GAPS

Dissertation submitted to the Entomology Graduate Program of the Universidade Federal de Viçosa in partial fulfillment of the requirements for the degree of *Magister Scientiae.*

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VIÇOSA - MINAS GERAIS
2022

Ficha catalográfica elaborada pela Biblioteca Central da Universidade Federal de Viçosa - Campus Viçosa

T

C697r
2022

Collares, Lara Jardim, 1998-

Literature survey and meta-analysis of phytochemicals as insecticides: trends and knowledge gaps / Lara Jardim Collares. – Viçosa, MG, 2022.

1 dissertação eletrônica (30 f.): il. (algumas color.).

Texto em inglês.

Orientador: Raul Narciso Carvalho Guedes.

Dissertação (mestrado) - Universidade Federal de Viçosa, Departamento de Entomologia, 2022.

Inclui bibliografia.

DOI: https://doi.org/10.47328/ufvbbt.2022.481

Modo de acesso: World Wide Web.

1. Inseticidas vegetais - Bibliografia. 2. Fitoquímicos. 3. Insetos. I. Guedes, Raul Narciso Carvalho, 1967-. II. Universidade Federal de Viçosa. Departamento de Entomologia. Programa de Pós-Graduação em Entomologia. III. Título.

CDD 22. ed. 632.9517

Bibliotecário(a) responsável: Bruna Silva CRB-6/2552

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APPROVED: June 27, 2022.

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ACKNOWLEDGEMENTS

Agradeço ao movimento feminista pelos direitos conquistados.

Agradeço aos meus pais por serem meu porto seguro.

Agradeço aos meus avós pelo amor incondicional.

Agradeço ao meu amor e parceiro de vida, Rafael e sua família.

Agradeço à minha rede de apoio, boa parte composta por mulheres e cientistas incríveis, em especial: Iare, Lay, Vica, Carol e Ju.

Agradeço à minha psicóloga, Ketelyn, por me guiar para o autoconhecimento.

Agradeço aos colegas de trabalho do Laboratório de Ecotoxicologia, da Oxitec e da G.A.C. Consultoria.

Agradeço a todos os professores, profissionais e colegas que me ajudaram nessa jornada, em especial: Raul, Léo, Terezinha, Karina, Davi, Seu Manoel, Diego e Eliane.

Agradeço ao Departamento de Entomologia da UFV e às instituições de fomento à pesquisa.

Ao Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), pela concessão da bolsa de estudos.

À Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG), pela concessão da bolsa de estudos.

À Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), pela concessão da bolsa de estudos.

Sou grata a fase do mestrado por ter aberto minha mente à novas oportunidades.

“Somos o que fazemos, mas somos, principalmente, o que fazemos para mudar o que somos”.

(Eduardo Galeano)

ABSTRACT

COLLARES, Lara Jardim, M.Sc., Universidade Federal de Viçosa, June, 2022. **Systematic literature review and meta-analysis of phytochemicals as insecticides: trends and knowledge gaps.** Advisor: Raul Narciso Carvalho Guedes. Co-advisers: Leonardo Morais Turchen, Karina Dias Amaral and Terezinha Maria C. Della Lucia.

To understand the context, the biases, and knowledge gaps of research with insecticides of botanical origin, this literature review was carried out assessing 76 years of research and covering 4,780 scientific articles for qualitative and quantitative analyses, including three meta-analyses. The study pointed out that the main botanical insecticides belong to the following major chemical groups: terpenoids, terpenes and carbonyl, which were all mainly tested in Coleoptera, Lepidoptera and Diptera insects. The survey also shows that despite the exponential growth of publications over the years, there are some biases and gaps that require attention. The evident focus on mortality estimates neglects the assessment of sublethal effects. In addition, most studies use only one group of species as experimental models (stored grain pests), which limits the applicability and representativeness of the results and information generated. As a result, the most common mode of exposure is by fumigation and contact. Thus, there is a predominance of estimates of lethal concentrations rather than lethal doses in these studies. Therefore, based on the evidence gathered, we recognize the need of studies with a broader range of insect species and the need to identify and characterize the molecules responsible for the insecticidal effect. This will allow us to circumvent current biases and recognize the main patterns of the relationship between the origin and structure of phytochemicals and their physiological and behavioral effects on insects.

Keywords: Botanic molecules. Insect. Review.

RESUMO

COLLARES, Lara Jardim, M.Sc., Universidade Federal de Viçosa, junho de 2022. **Revisão sistemática da literatura e meta-análises de fitoquímicos como inseticidas: tendências e lacunas do conhecimento**. Orientador: Raul Narciso Carvalho Guedes. Coorientador: Leonardo Morais Turchen, Karina Dias Amaral e Terezinha Maria C. Della Lucia.

Para compreender o contexto, os vieses e as lacunas de conhecimento das pesquisas com inseticidas de origem botânica, esta revisão de literatura foi realizada avaliando 76 anos de pesquisa e abrangendo 4.780 artigos científicos para análises qualitativas e quantitativas, incluindo três meta-análises. O estudo apontou que os principais inseticidas botânicos pertencem aos seguintes grandes grupos químicos: terpenóides, terpenos e carbonila, todos testados principalmente em insetos Coleoptera, Lepidoptera e Diptera. A pesquisa também mostra que apesar do crescimento exponencial das publicações ao longo dos anos, existem alguns vieses e lacunas que requerem atenção. O foco evidente nas estimativas de mortalidade negligencia a avaliação dos efeitos subletais. Além disso, a maioria dos estudos utiliza apenas um grupo de espécies como modelo experimental (pragas de grãos armazenados), o que limita a aplicabilidade e representatividade dos resultados e informações geradas. Como resultado, o modo mais comum de exposição é por fumigação e contato. Assim, há uma predominância de estimativas de concentrações letais ao invés de doses letais nesses estudos. Portanto, com base nas evidências reunidas, reconhecemos a necessidade de estudos com uma gama mais ampla de espécies de insetos e a necessidade de identificar e caracterizar as moléculas responsáveis pelo efeito inseticida. Isso nos permitirá contornar os vieses atuais e reconhecer os principais padrões da relação entre a origem e a estrutura dos fitoquímicos e seus efeitos fisiológicos e comportamentais nos insetos.

Palavras-chave: Moléculas botânicas. Inseto. Revisão.

SUMMARY

INTRODUCTION

"If we want to understand where good ideas come from, we have to put them in a context" (Steven Johnson, 2011). The context attributes meaning, solves investigations, diagnoses patients, and avoids fake news. Understanding the context allows us to draw a line of correlations on space and time.

Drawing the timeline of processes is the first step to tell a good story about a theme. That is exactly what a literature survey and review does. The literature review gathers scientific evidence and tells us one out of the various stories that can be told. To tell this story and gather the facts, meta-analysis is also used, as a tool that statistically integrates the results of independent studies and synthetizes them in only one view that can be easily interpreted (Gurevitch 2020; Chueke and Amatucci 2022).

Several reviews and meta-analyses have already been published using insect control and pointed out the importance of synthetic insecticides for agriculture and public health (e.g., Cooper e Dobson 2007; Nauen et al. 2007). However, the harm that arises from the indiscriminate use of these synthetic pesticides, such as environmental contamination (Albuquerque et al. 2016; Vieira et al 2016; Mansouri et al 2017), residues in food (YANG et al. 2019; Caldas et al. 2011; Avancini et al. 2013) and selection of resistant insect populations (Silva et al. 2016; Ribeiro et al. 2017, Guedes et al. 2020), is also important. Thus, it is extremely important the permanent search for insecticidal substances that cause less environmental and social impact, aiming for a more sustainable agriculture.

Botanical substances have been studied as an alternative to synthetic insecticide (Ansante et al. 2015; Turchen 2016; De Cássia Domingues et al. 2020; Maia et al. 2020) because they are perceived as exhibiting lower toxicity to mammals, greater selectivity and safety for non-target organisms, lower risk of resistance development and lower environmental persistence (Rosell 2008; Glare 2012; Seiber 2018). However, recent reviews pointed out some limitations of studies on botanic insecticides and a consequent appeal for evidence and information within this subject (Turchen, Cosme-Júnior, Guedes 2020; Khalid et al. 2020).

The insecticide and/or repellent effect of plants in insects is the result of the evolution of various defense mechanisms of these plants, acting together in the attempt to reduce the harm that can be generated by phytophagous insects (Talk Gajger and Dar 2021). Therefore, botanical molecules can be potentially used as insecticides, or as model for the synthesis of new insecticidal molecules, or yet they can be structurally modified resulting in new ones, efficient for pest control (Xu et al 2016); a classic example are the pyrethroids that developed in since the 1960's from pyrethrins obtained from chrysanthemum flowers.

Therefore, this work aimed to survey the studies and contextualize the world research scenario of botanical insecticide molecules using a systematic literature survey and meta-analyses. The article also sought to recognize which chemical groups the main insecticide substances of botanical origin belong to and recognize the main convergence and gaps among the studies carried out so far within this subject.

MATERIAL AND METHODS

Data collection

This study followed the PRISMA approach for the systematic literature survey (Moher et al 2006). The systematic review and meta-analysis followed the steps of identification, screening/elimination, eligibility and inclusion.

The database used was Web of Science from 1945 to April 2021. The search was performed with the following keywords: "bioinsecticide" or "extract" or "phytoinsecticide" or "essential-oil" or "natural molecules" or "natural compounds" or "botanical insecticide" or "pesticide", in mandatory combination with the words "insecticidal activity" or "insecticide" and the word "insect". Only scientific articles published in English in peer-reviewed journals were retained.

Screening

The initial dataset compiled was used for basic screening based on the following exclusion criteria: review and/or comparison articles; articles with restricted access or duplicates; articles with incomplete information. Subsequently, the manuscripts were selected, based on their titles and abstracts, using the following the inclusion criteria - address the toxicity of isolated botanical substances on insects.

For eligibility, the articles underwent a second screening (full text) to exclude studies that did not establish or present dose/mortality and/or concentration/mortality relationships. Articles without sufficient statistical data were also excluded, as well as those that were not relevant to the research objective focused here.

Data extraction

For each publication, the following information was recorded: doi; article title; publication date; geographic coordinates of the article's first author's address; species of plant(s) from which the substance is derived; plant family(s); substance(s) studied; studied insects; insect order; developmental stage of the insect(s); instar of the insect(s); presence of sublethal effect; presence of transgenerational effects; exposure route; parameter type (DL or CL); DL or CL value(s); confidence interval value(s); and number of subjects in the control treatment.

The recorded substances were classified following the group proposed by Egbuna et al. (2018): Phenolics; terpenes; terpenoids; organonitrides; organosulfides; and others. The aromatic (non-phenolic) and carbonyl classes were also added to group the other substances (Table 1).

Table 1. Chemical classification of substances

Classes	**Representative constituints**
Phenolics	Polyphenols; aromatic acid derivatives
Aromatics	Non-phenolic aromatics
Terpenes	Monoterpenes; Sesquiterpenes; Diterpenes; Triterpenes; Polyterpenes
Terpenoids	Carotenoids; Xanthophylls; Triterpenoid; Steroids
Organonitrides	Alkaloids; Cyanogenic glucosides; Nonprotein amino acids
Organosulfides	Allicin; Alliin; Piperine; Glutathione; Phytoalexins
Carbonyl	Substances with the carbonyl group
Others	Phytic acid; Oxalic acid; Tartaric acid; Malic acid; Quinic acid

Only papers that had toxicological endpoints with units convertible to ppm (94 articles) were used in the quantitative meta-analyses to allow direct comparisons and testing. For the other analyses, the data resulting from the filtering were all used.

Statistical analyses

A binary meta-analysis was used to test the chances of evaluating sublethal effects. Within this context, the odds ratio and 95% confidence intervals were used to determine the overall effect measured, where the odds ratio is the probability of an outcome between two alternatives. These estimates were submitted to formal meta-analysis with a random effect model considering chemical classes as a group, and insect orders as a subgroup. The quantification and heterogeneity-test (i.e., Q, H, and I^2) were conducted, and the inverse variance and DerSimonian–Laird methods were used to estimate the between-study variance (τ^2). Studies with $n \leq 1$ event in both groups were excluded from meta-analyses.

Two additional quantitative meta-analyses were used to quantify lethal doses and concentrations among different exposure methods and chemical groups. Lethal dose (LD_{50}) or lethal concentration (LC_{50}) and 95% confidence intervals were used to determine the median values in the exposure methods and chemical groups. In this case, the LC50 or LD50 data were converted to units of ppm and transformed by a natural logarithm to allow for comparison.

All analyzes were carried out using software version R. 3.5.1 (R Development Core, Vienna, Austria) with the packages “meta”, “metafor” and “stats”. The graphical illustrations (qualitative and quantitative) were produced with Wacom creative table (Intuos S, Tokyo, Japan) using Corel Painter (Essential 7, Ottawa, ON, Canada).

RESULTS

The literature survey in the Web of Science database resulted in 4,780 articles, but after the initial filtering, the number was reduced to 4,204 articles, which were subsequently screened based on titles and abstracts. Of these selected articles, 550 articles met our initial selection criteria and were subjected to full-text screening. One hundred and thirty-eight (138) papers were deemed as suitable for the purposes of the desired qualitative and quantitative analyses (Figure 1)

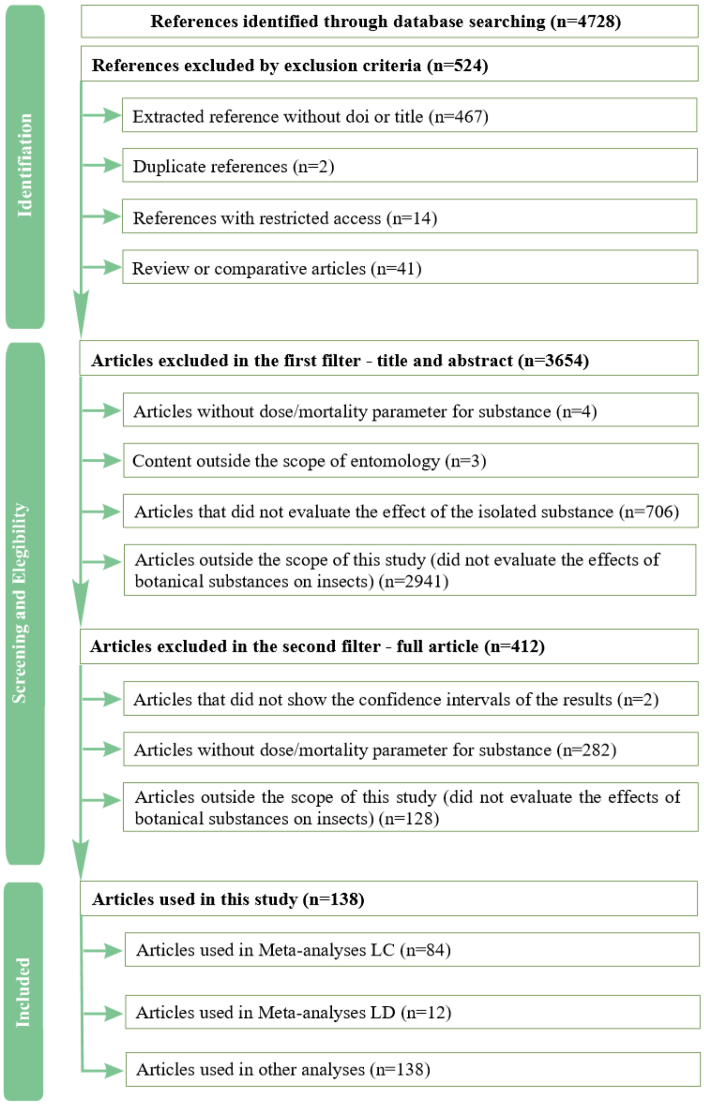

Figure 1. Flowchart diagram describing the steps of filtering data from scientific papers obtained from the systematic literature survey review using the Web of Science database (1945-April 2021).

Authors of studies evaluating the effects of insecticidal molecules of botanical origin were mainly from Asia, especially China. The results showed that Asia is the continent with the largest number of researchers and the largest number of substances studied. On the other hand, researchers from Africa and Europe published little on the subject, only seven and eight articles from these countries, respectively. None of the studies analyzed originated in Oceania (Figure 2).

Although Europe publishes more than Africa, African publications have a greater number of substances studied per publication. The average number of substances studied per article in the world is 4.19 substances, while in Africa this average is 5, in

Asia it is 4.8, in Europe it is 3.4 and in the America an average of only 2.5 substances are studied per article (Figure 2).

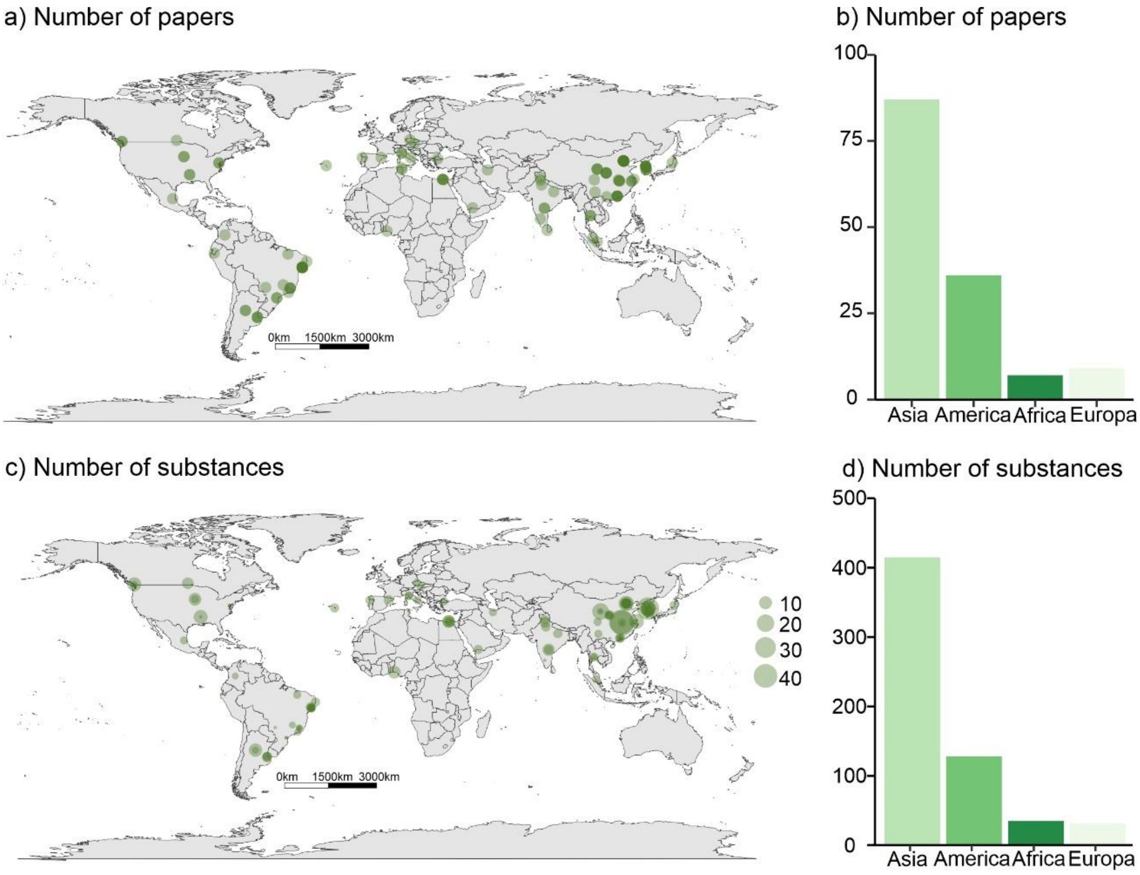

Figure 2. (a) Maps and bar plots identifying the geographic distribution of the first author of published articles that were used in this research. (b) Number of works produced by authors from each continent. (c) Bubble chart map indicating the number of substances studied by region. (d) Number of times that substances of botanical origin were studied by authors from each continent.

The first article published in the period of analysis was in 1993. In the following five years, no article was published and 84% of all articles analyzed were published after 2010 (Figure 3).

The most studied class of insecticidal substances so far studied are terpenoids 34% followed by terpenes 23.2% and carbonyl 16.4%. The least studied class are organonitrides (2%) and others (2.8%).

Figure 3. Scatterplot of number of articles with the chemical group published per year. (o que significam os tamanhos diferentes?)

Research with insecticidal molecules of botanical origin involved mainly insects of the Coleoptera order (42%). Compounds from 35 botanical families were studied, with Lamiacea, Asteraceae and Rubiacea being the families with the most substances studied, respectively (Figure 4). Overall, the studies were diversified, testing compounds originating from different families in the same insect order.

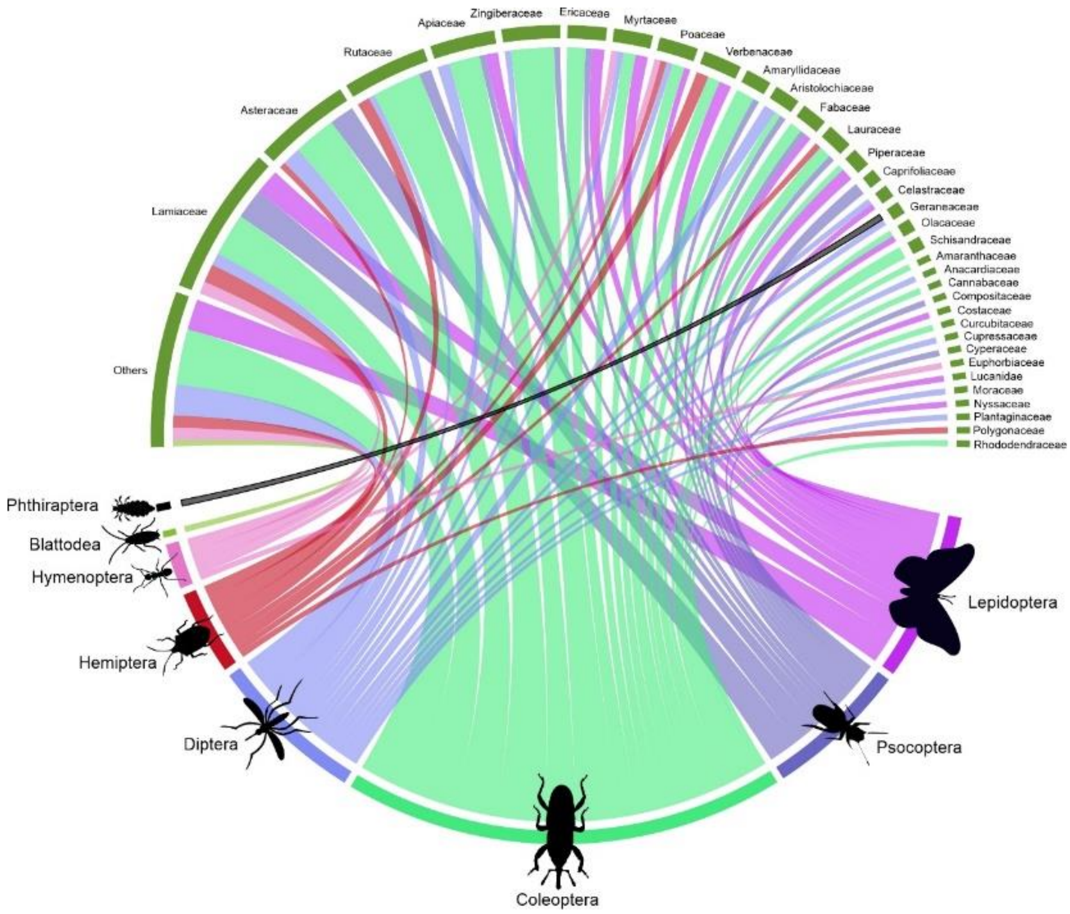

Figure 4. Interaction between the diversity of plant families and insect orders studied from the bibliographic survey of articles on insecticidal molecules of botanical origin; the thickness of the bar and line under each order/family connecting them corresponds to the relative number of articles dealing with said insect groups and molecules derived from plant groups. (n= numero de paper que foram usados para essa figura?).

Eighty seven percent (87%) of the studies assessed substances from the terpenoid, terpene, carbonyl or phenolic groups, 73% of which belong to the terpenoid and terpene classes. The main insect orders studied were Coleoptera, Pscocoptera, Diptera and Lepidoptera, which correspond to 86% of the studies and encompassed all chemical groups (Figure 5).

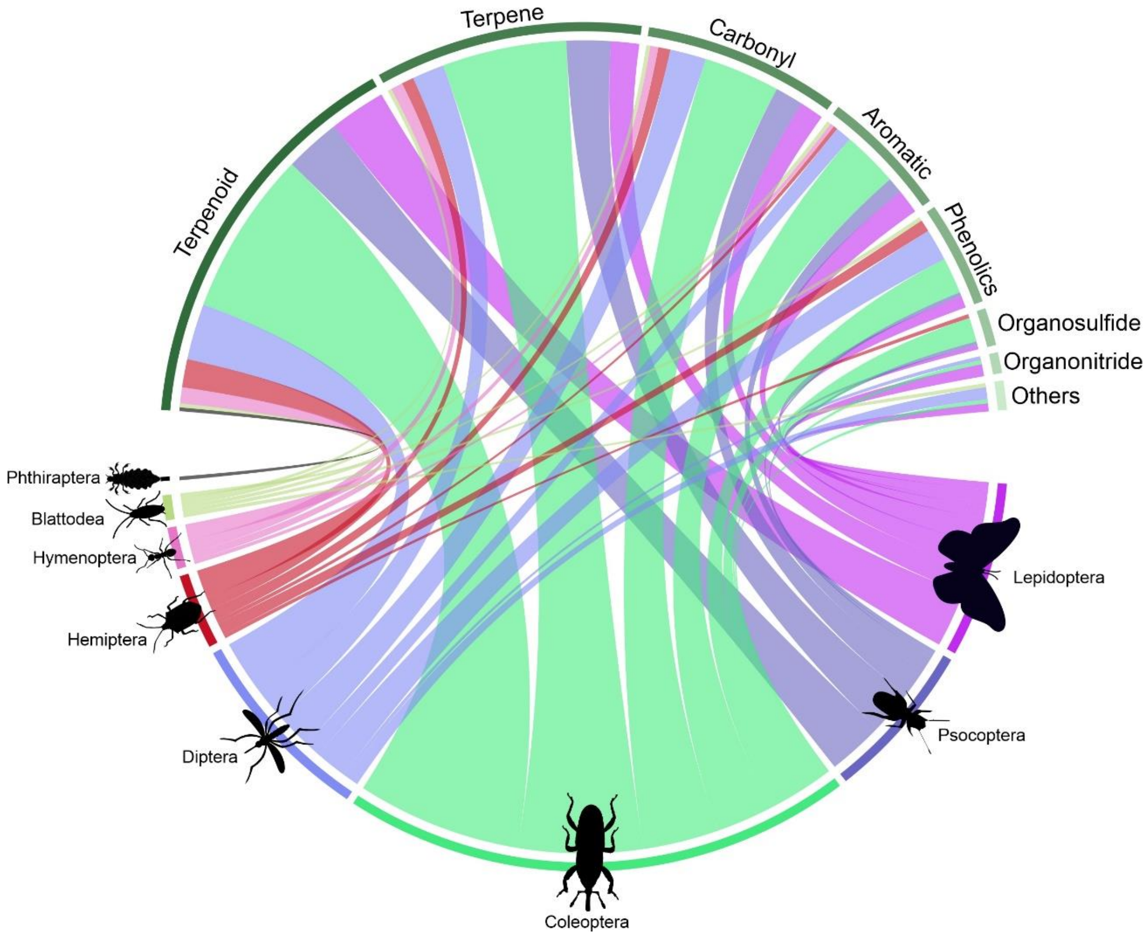

Figure 5. Interaction between the diversity of chemical groups of the insecticidal substances studied and the orders of insects tested based on the literature survey of articles on insecticidal molecules of botanical origin; the thickness of the bar and line under each chemical order/group connecting them corresponds to the relative number of articles dealing with said insect groups and chemical groups (n= numero de paper que foram usados para essa figura?).

The most frequent method of exposure observed in the studies screened were fumigation, followed by topical exposure, contact and finally ingestion. Fumigation was used for testing almost half of the analyzed substances (48%) and was present in 39% of the articles surveyed (Figure 6).

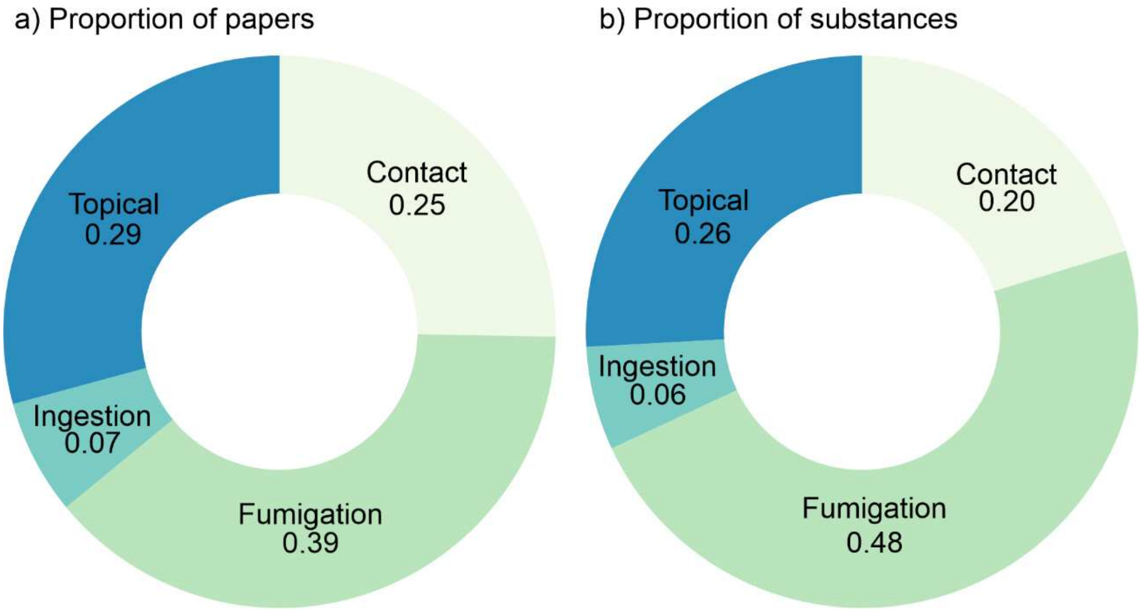

Figure 6. Types of exposure route present in the experiments of the analyzed articles. (n= percentage of papers and substances)).

The low incidence of tests for sublethal effects in studies with insecticidal substances of botanical origin was subjected to subsequent analyses to detect whether the perceived bias was restricted to some insect orders and/or some chemical group of substances, or if the trend was general (Figure 7).

The global effect estimated by the meta-analysis confirmed that the sublethal effect of substances of botanical origin was almost never tested (i.e., RR = 0.34; z = -4.8; P > 0.001). When the subgroups are analyzed individually - terpenoids, phenolics and organonitrides, it is statistically evident that the sublethal effects are not a target of attention, while the combined estimates of the other substance subgroups were not statistically significant either. O que isso nos diz? (descreva brevemente)

The overall effect of the dataset exhibited low heterogeneity between chemical groups (I^2 = 9%). However, a median heterogeneity (between 19% and 49%) was observed in the subgroup of terpenes, carbonyl and phenolics. This is because the studies evaluating this effect were carried out mainly in the orders Lepidoptera and Psocoptera.

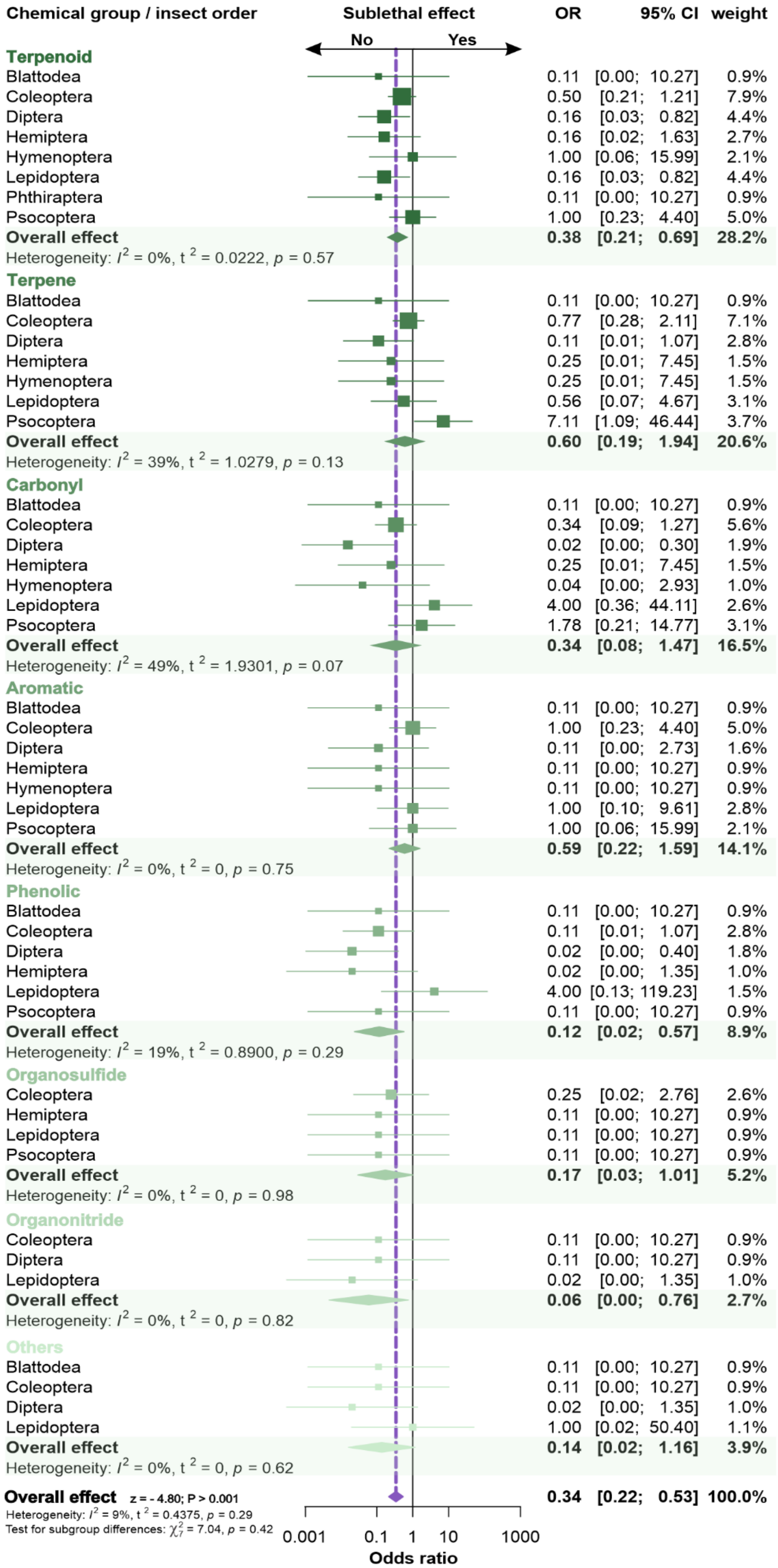

Figure 7: Binary meta-analysis evaluating the existence or not of sublethal effect in articles that evaluated the insecticidal effect of botanical substances. The meta-

analysis is divided into chemical groups into which the substances were classified and into the orders (subgroups) into which the insects were classified.

Additional meta-analyses were performed to recognize whether the potency or toxicity of the insecticidal substances of botanical origin (represented by their chemical groups and their LC50's) varied with their mode of exposure, if by contact, fumigation, ingestion and topical. The general trends estimated by a random model in meta-analysis (see purple diamond) show that lethal concentrations of insecticidal substances of botanical origin were greater than 1 ppm, being approximately 20 ppm (general effect = ln 3.00) (Figure 8).

When the subgroups are analyzed individually, it is apparent that topical exposure and ingestion followed the overall effect not exhibiting significant difference among phytochemical groups. Nonetheless, the response was heterogeneous varying among modes of exposure. Thus, such differences were significant among phytochemicals for fumigation and contact, and the effect of the different chemical groups was heterogeneous (100% and 89%, respectively), especially due to the low toxicity exhibited by organosulfides and the others compounds.

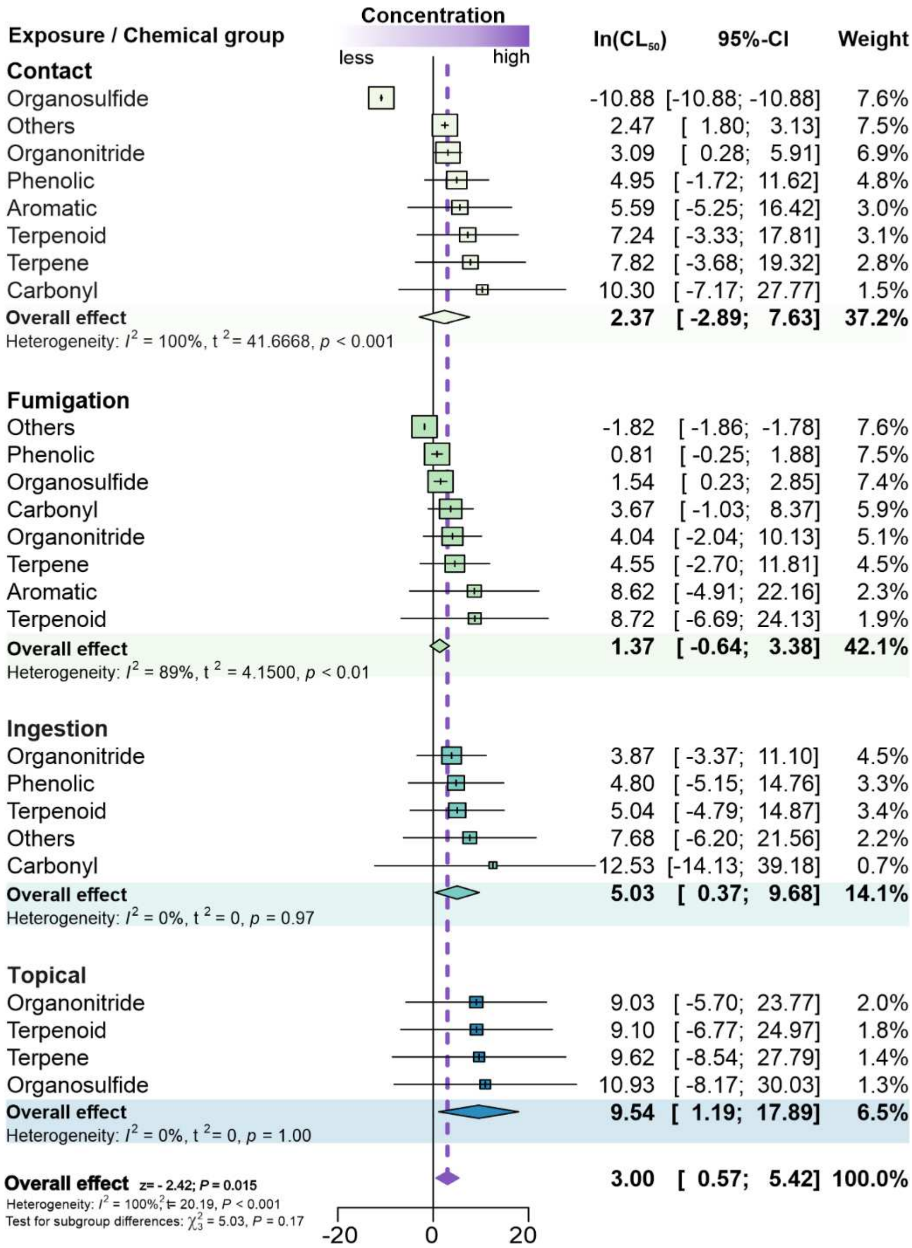

Figure 8: Quantitative meta-analysis comparing the LC50's, as toxicity endpoints in papers that evaluated the insecticidal effect of botanical substances. The meta-analysis is divided into chemical groups into which the substances were classified and into the orders (subgroups) into which the insects were classified. Concentrations (ppm) were transformed by natural logarithm. O que significam os quadrados, losangos e barras ? A legenda precisa ser bem informativa.

Another meta-analysis was carried out with the same purpose as the previous one, but now to recognize whether the toxicity determined through LD50 estimates of insecticidal substances of botanical origin (represented by their chemical groups) was different in the different modes of exposure: contact, fumigation and topical. As for LD50, the general trends estimated by random model in meta-analyses (see purple diamond) show that lethal doses of insecticidal substances of botanical origin were greater than 1 ppm, approximately 18 ppm (general effect= ln 2.88); they were similar for all exposure routes. This can be explained by the lack of work using LD50, regardless of the chemical group used as the source of the substance (Figure 9). The overall toxicity among phytochemicals was not significant, but there was significant variation among modes of exposure. Therefore, when each mode of exposure was individually considered, the response to fumigation was prevalent and accounts for 89% of the determinations.

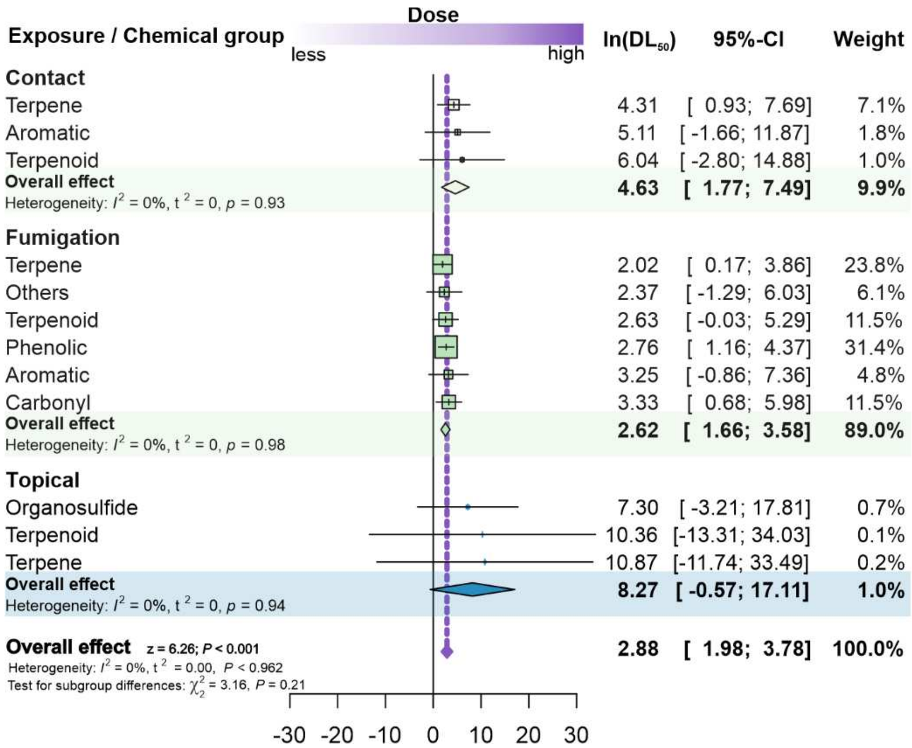

Figure 9. Quantitative meta-analysis comparing LD50 in articles that evaluated the insecticidal effect of botanical substances. The meta-analysis is divided into chemical groups into which the substances were classified and into the orders (subgroups) into which the insects were classified.

DISCUSSION

During the systematic literature survey, about 15% of the articles collected from the database were not used in this work because they did not evaluate isolated substances. This result shows a frequent concern of the scientific community due to the lack of information about the chemical characterization of the molecules responsible for bioactivity (Isman and Grieneisen 2014).

The search for active botanical substances against insects is intensive, time consuming, multidisciplinary and complex. Therefore, much research is not completed by the individual research groups, especially in countries where the scientific career is not stable, and the number of publications is reduced as research advances in the characterization of the substance responsible for the insecticide effect is more expensive and time-consuming (Lopes 2017).

The growing search for new more sustainable bioactive molecules resulted in the increase in the number of articles published annually with the characterization of insecticide molecules of plant origin (Isman and Grieneisen 2014; Turchen, Cosme-Júnior and Guedes 2020). Such molecular characterization studies were not always tangible, so the oldest studies eligible for this bibliographic review were published in the 1990s, coincidentally or not, when chromatography became more accessible (Scott 2020).

The origin of the articles also reports a public concern with the unequal distribution of global scientific publications. According to Isman and Grieneisen, (2014), between 1980 and 2012, the country that most published articles related to botanical insecticides was China, followed by India and Brazil, respectively. China's contribution to research (and patents) about molecules of botanical origin is large, especially because of government, economic and bureaucratic incentives for this to happen (Simmonds et al. 2020). Such information may explain the result of the present work that points to a large amount of studies with isolated botanical substances published from Asia.

In America you can highlight the enormous potential for discovering new molecules. In Brazil, more than 50,000 chemical structures from plant metabolism were elucidated, and the total number exceeds 100,000 structures (Wink 2006). Although only a small portion has its insecticide activity evaluated, it was enough for Brazil to appear as the country that houses most of the continent's research on the theme analyzed in this study.

Beetles are the main insects used as a model of toxicological studies with insecticide substances (Silva et al. 2020; Anukiruthika, Jian and Jayas 2021). Although this order is the most diverse, 100% of the coleoptera work evaluated in this review studied stored grain pests. Of this amount, 80% used the following four species: *Tribolium Castaneum*, *Lasioderma Serricorne*, *Sitophilus zeamais*, *Sitophilus oryzae.*

This data brings valuable information on the excessive use of experimental models, which, although important in validating methods, generates a bias about the representativeness and scope of the research carried out so far. The recurrence of studies with such species is due to the short life cycle, low production cost and/or large number of studies on the biology and behavior of these beetles (Campbell et al. 2021). Therefore, it is necessary to use different species and insect orders in the testing of the same substance to validate the different sites and modes of action and their different effects (targeted and non-targeted).

Despite the most common screening tests use topical application tests (Gomes et al. 2016) or food intake containing the active ingredient by insects (Alves et al., 2012; Carvalho et al., 2015), meta-analysis detected that for toxicological tests with insecticides of botanical origin, the predominant exposure methods are fumigation and contact. Once again, the perceived bias of use of stored grain pests is a justification, as these are the main exposure methods employed in studies with this group of insects.

Insecticide uptake by insects varies with the different types of exposure. (Shivanandappa and Rajashekar 2014). Therefore, it is important that insecticide compounds are tested through different modes of exposure. Possibly, the low efficiency of penetration through topical application and the requirement of higher doses for ingestion bioassays are limiting the use of these modes of exposure when compared with fumigation or contact.

In this context, the importance of obtaining dose-response or concentration-response curves is necessary to record the toxicity and thus potency of the compounds under testing (Tsatsakis et al. 2018). It is noteworthy that exposure to situations in which the dose absorbed by the insect body can be calculated is important to understand the magnitude of the physiological response (Cutler 2013).

A problem already reported in the literature is the difficulty in qualitatively correlating the results of research that assess the relationship between chemical structure and insecticidal effect. Since interspecific differences or differences in the developmental stage of the same species may be associated with differences in susceptibility to insecticidal substances (Viegas Júnior 2003). In addition, it is rare for research to address the binding sites, mode of action and chemical characteristics of the molecule relating to its physiological effect. Nonetheless, a large number of studies evaluated the effect of substances derived from essential oils in terms of toxicity against different insect species (Turchen, Cosme-Júnior and Guedes 2020). Essential oils are mostly made up of terpenes or its derivatives (Viegas Júnior 2003; De Matos et al 2019; Noriega 2020). Consequently, terpenes were the chemical group most studied in the articles analyzed in this work.

Some terpenes protect the plants that produce them, such as limonene (Mursiti et al 2019), one of the substances studied in the analyzed articles. Studies show the acetylcholinesterase inhibitory action in insects caused by this chemical group (Al-Nagar et al 2020). In addition, research indicates that in the period in which plant species accumulate terpenes, their leaves are less preyed upon than in periods with low terpene accumulation, which suggests that the substances may be related to the plant repellency and toxicity to herbivores leading to their avoidance by these organisms (Ninkuu et al 2021).

Terpenoids, on the other hand, are oxygenated derivatives of terpenes and are also extensively researched for their insecticidal action. Some effects caused by this chemical group on insects, reported in the literature, are: damage to fertility and fecundity, activities as inhibitors or growth retardants, damage to maturation (Abou-Taleb 2016, Plata-Rueda et al 2020, Tak and Isman 2017).

Among the most researched plants as a source of insecticidal substances is *Azadirachta indica*, a source of many terpenes and terpenoids, including azadirachtin. The substance belongs to the group of limonoids and is one of the most studied insecticidal compounds of botanical origin currently, with phago-deterrent activity, inhibiting feeding and egg laying, negatively affecting growth, development and metamorphosis and preventing ecdysis (Passos et al 2019, Muhammad and Kashere 2020). Currently, some products available on the market as insecticides contain azadirachtin as a main active ingredient (Pavela 2016).

In the carbonyl group are esters, ketone, amide, aldehydes, carboxylic acids, pyrethrins and other compounds. Many of these have already demonstrated insecticidal activity, although the insecticidal characteristic is not always attributed to the carbonyl group. However, in the case of ketones the orbital electronegativity of the carbonyl group was reported as the main parameter responsible for the inhibition of acetylcholinesterase (Herrera et al 2015). Carboxylic acids can act through the mode of action of soaps, compromising the waterproofing of insects (Pessoa et al 2017). The insecticidal properties of pyrethrins derive from their ability to alter the function of sodium channels, thus interrupting electrical signaling in the nervous system. A classic example of pyrethrins is the pyrethroid group of insecticides, which are synthetic analogues of pyrethrins (Henrich 1994).

The phenolic class includes phenols, encompassing lignin isoflavones, anthocyanins, rotenoids and tannins. Rotenoids have an insecticidal action with an effect on respiration, causing the insect to die. Tannins alter the functioning of the metabolic system and reduce the growth rate. In addition, phenols can induce early metamorphosis in some arthropod species and impair their development (Chen et al 2018, Lopes et al 2017, Furstenberg-Hagg and Zagrobelny 2013, Mitchell et al 2016).

Despite the diverse groups of phytochemicals targeted for the recognition of insecticidal activity, the prevailing attention to mortality as toxicological endpoint and overemphasis on stored product beetles are important biases to consider, together with the lack of studies on non-targeted species. Finally, another alarming scientific concern reported from the results of this work is the absence of a statistical relationship between dose/concentration and mortality in many studies. This is surprising since the establishment of dose or concentration-response relationships is the basis of recognition of biological activity of any given compound jeopardizing the effort when such assessment in not included in the study.

CONCLUSION

The work presented here recognizes the existence of an impressive growth of studies with insecticides of botanical origin, however, biases and knowledge gaps were identified through meta-analyses.

There is an excessive use of few insect species for the evaluation of the bioactivity of the insecticides in the evaluated articles. The prevalent use of stored grain pests for toxicological testing affected the trends observed favoring prominence of exposure by fumigation. In addition, the response usually assessed is mortality with wholly neglect of sublethal effects.

The above evidence, added to the large number of studies that did not identify the protagonists of the insecticide effect, leads us to conclude that there is need for new components to be included in the studies. It is necessary to evaluate a broader range of insect species and chemically identify the substances responsible for different insecticidal effects (i.e., beyond mortality). Thus, it would be possible to reduce the biases and better understand the most promising phytochemical groups with potential for the development of novel insecticide molecules.

ACKNOWLEDGMENTS

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