

QUANTITATIVE STUDY ON ANTI-PEST ACTIVITY OF NATURAL PRODUCTS BASED ON VISUALIZATION FRAMEWORK OF KNOWLEDGE GRAPH

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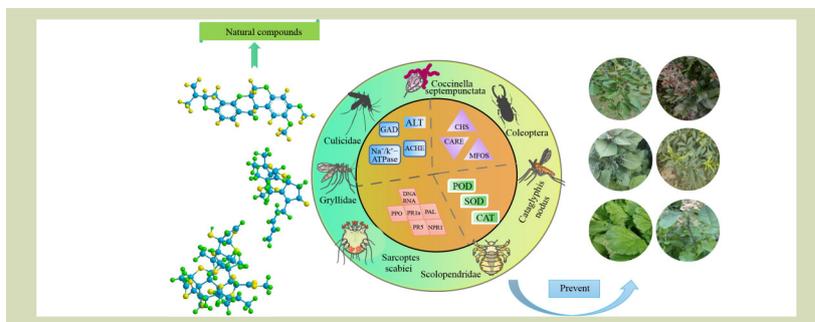
KEYWORDS

anti-pest activity, crop protection, insect pest, natural product, visual analysis

HIGHLIGHTS

- Using visual analysis to predict the trend of natural product pest resistance.
- Summarized the anti-insect activity and mechanism of natural products.
- Natural compounds insecticide will be the general trend.

GRAPHICAL ABSTRACT



ABSTRACT

To help in the prevention of large-scale loss of agricultural production caused by crop pests, a visual analysis was performed on the main research areas, key countries, organizational cooperation, citation sources and current trends in pest research by searching the literature of Web of Science database and using CiteSpace 5.8.R3 and VOSviewer 1.6.18 software. Additionally, the effects and mechanisms of natural products with anti-insect activity were summarized through visual analysis. According to the bibliometric analysis, keywords such as mortality (232 occurrences), natural enemy (232 occurrences) and spinosad (110 occurrences) were common, and insecticides and natural enemies of pests were the main methods for killing pests. However, pesticide use exhibits numerous limitations. Co-occurring terms in visualization analysis mainly included residue (193 occurrences), detection (153 occurrences), degradation (133 occurrences), recovery (103 occurrences), pyrethroid (97 occurrences) and pesticide residues (65 occurrences). Thus, pesticides cannot fundamentally solve food security; pesticides also pollute the environment and endanger

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human health. Therefore, green and efficient pesticides that can replace synthetic pesticides are urgently needed. Natural products have recently gained attention in Brazil, China, the USA and other countries because they are green and pollution-free, and new natural pesticides have been developed. This visual analysis combined data mining with literature review and summarize the anti-pest activities and mechanisms of action of natural products. This information provides a foundation and ideas for researchers to study the application and development of natural products in pest control.

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1 INTRODUCTION

According to a United Nations forecast, the number of hungry people will exceed 840 million by 2030 (9.8% of the global population). This statistic shows that insufficient food supply has become a global problem. One of the main reasons for this phenomenon is the pests affecting the crops. According to statistics, approximately 10% to 16% of the annual crop yield in the world is lost to pests^[1]. Since pests, such as insects, can identify acceptable host plants, develop and reproduce based on the light intensity, color, humidity, nutrition and information chemistry from host plants^[2], a variety of pesticides that can adopt different pest control strategies have been developed^[3]. Although they are characteristically fast-acting, cost-effective, easy to use, and contribute considerably to improving crop yield and quality, the concerns and problems persist^[4]. For example, less than 0.1% of the insecticides are effective toward target pests, adversely affecting the non-target species^[4,5]. In addition, long-term excessive use of pesticides increases the nitrogen and phosphorus content in the soil, resulting in the loss of water, which impacts the growth of crops for years. It also causes air and water pollution and affects human health^[6,7]. Therefore, to protect the ecological environment and human health, it is necessary to find natural products, which are non-toxic, pollution-free and effectively control crop pests.

Natural products have diverse structures and strong biocompatibility, and are environmentally friendly, and consequently provide an indispensable lead compound library for the development of insecticidal drugs^[8]. Their sources range widely from plants and animals to microorganisms^[9]. As early as 2000 years ago, China started using plants to kill insects. According to *Zhou Li*, *Illicium lanceolatum* was used to kill insects. There have been records about plants being used to kill insects in *Shennong Bencao Jing*, the compendium of *Materia Medica*, and *Tian Gong Kai Wu*, but people were unaware that natural plant products were used to kill plant

insects^[10]. Now there are more reports on the insecticidal effectiveness of natural products, including alkaloids, flavonoids, terpenoids, and phenols^[11-14]. They exhibit certain anti-insect activities against pests such as beetle^[15], *Aedes aegypti*^[16], *Plutella xylostella*^[17] and others, and can potentially be used as natural insecticides^[18]. At present, the most common natural anti-insect products in the market are pyrethroid^[19], rotenone^[20] and azadirachtin^[21]. Natural products mainly act by interfering with the growth and development of pests, thereby affecting their digestive system, respiratory system and nervous system. In addition, natural products can affect the enzyme activity in insects through amphotericin B^[22], Na⁺/K⁺-ATPase^[23,24], P450 enzyme^[25,26], carboxylesterase^[27,28], glutamic acid decarboxylase^[29-31], chitinase^[32] and other factors, which finally achieves the aim of killing pests^[33]. These special natural products are non-polluting, relatively safe to humans and animals, and do not easily confer drug resistance to target organisms; therefore, they have been widely used in crop protection.

It is imperative to develop natural products with anti-pest activity. Therefore, the purpose of this review is to describe the chemical structure, anti-pest activity, and mechanism of natural products reported in recent years that exhibit protective effects on crops. This review contributes to developing solutions to some key problems the crop and food production industry faces and provides a theoretical basis for generating new anti-disease and pest drugs from natural products.

2 VISUAL ANALYSIS

Using the Web of Science database, we performed a literature search using the search terms “(natural products or botanical pesticides or green pesticides) and (insecticide or insect resistance or insect pest)” from 2017 to 2021. After exporting the literature, we used the Java application CiteSpace 5.8.R3 to

comprehensively analyze the keywords, research areas, and countries that published research on pests and diseases at home and abroad. The time slice was set to 1 and the other settings were set to default values. The results of visual analysis were illustrated using VOSviewer software. We performed strict statistical analysis to ensure that global natural product resistance trends were closely followed. Keywords are the core feature of this study, and these were used to identify key research areas in related fields. First, we used two network cutting-edge features of CiteSpace, namely “Pathfinder” and “Pruning the Tender Networks” to draw a keyword coexistence graph. The following three main factors were associated with research on the resistance of natural products: the insecticidal activity of natural products and their extracts, chemical composition of natural insecticides, and Coleoptera and other pests associated with pesticide resistance. High-frequency keywords are shown in Fig. 1. After this general analysis, we used VOSviewer 1.6.18 for detailed exploration, as well as to

analyze co-occurring keywords and for thematic clustering analysis. VOSviewer 1.6.18 big data identified 62,716 keywords in the included literature. Initially, 1189 keywords with an occurrence frequency of more than 15 were selected. We next screened the 60% of the keywords with the closest relationship, and 713 keywords related to natural product resistance to insect pests were selected. The negative effects of pests on humans has gained the interest of researchers worldwide. Researchers are committed to countering these pests while minimizing environmental damage. In combination with the green area in cluster 2 of keywords identified in bibliometric analysis, research has mainly focused on the impacts of different pesticides on the ecological environment. According to published literature, when using synthetic pesticides, early insecticide targeting is low and pesticide pollution and harm are much more serious compared to the effects of fungicides and herbicides. In addition, some pesticides have long-term toxic effects and long incubation periods, exhibit strong

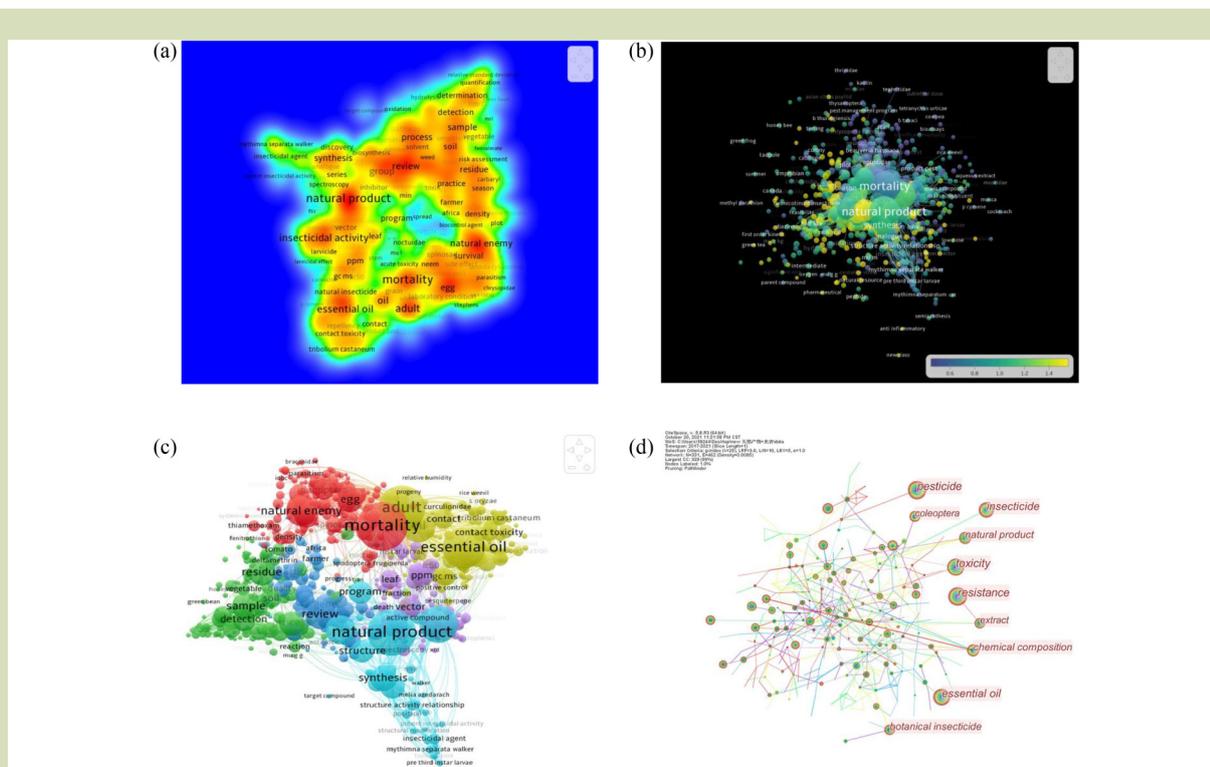


Fig. 1 High-frequency keywords in the research of natural compounds to control crop pests. Node size represents the strength of keywords and the links represent the connection between these keywords. (a) Density visualization of keywords. Orange and green areas represent frequent and infrequent keywords, respectively. Keywords are visualized using color changes from purple to yellow. A color closer to yellow indicates greater research attention, indicating a key research frontiers. (b) Overlay visualization of keywords. A larger value leads to a more yellow color, indicating a key research frontiers. (c) Network visualization of keywords, with different colors representing different clusters. (d) Prepared using CiteSpace 5.8.R3, showing the top 10 keywords. A larger circle displayed by keywords indicates a higher frequency of occurrence. The distance between keywords is positively correlated with the degree of closeness between them. Images (a–c) were prepared using VOSviewer1.6.18.

persistence in the environment, and are potentially harmful^[6].

Co-occurring words highlighted in visualization analysis mainly included residue (193 occurrences), detection (153 occurrences), degradation (133 occurrences), recovery (103 occurrences), pyrethroid (97 occurrences), pesticide residues (65 occurrences), carbaryl (46 occurrences), clothianidin (24 occurrences) and dimethoate (23 occurrences). Combined with the literature and visual analysis results, researchers first studied organophosphorus insecticides and acaricides such as dimethoate (Fig. 1). In humans, pesticides such as organophosphorus compounds enter the body and can cause harm to the skin, respiratory system and digestive system^[34–36]. Over time, the focus of researchers has shifted toward carbamate insecticides, such as carmine, which has a similar mechanism of action as organophosphorus pesticides^[37,38]. Acaricide is a new broad-spectrum insecticide and herbicide developed to overcome the limitations of organochlorine and organophosphorus pesticides^[39,40]. Given that its molecular structure is similar to those of natural products, it shows the advantages of easy degradation and small amounts of residue being left in the environment^[41,42]. Most representative drugs are less toxic than organophosphorus pesticides but still have carcinogenic effects^[43–45]. For pyrethroid pesticides, the synthesis of natural products has been simulated^[46,47]. Pyrethroids can be natural or synthetic, and their insecticidal toxicity is more than twofold higher than those of earlier-generation pesticides, such as organochlorine, organophosphorus and carbamates^[48,49]. However, repeated use of pyrethroids has led to cross-resistance^[50]. Neonicotinoid insecticides are fourth-generation insecticides developed after organophosphorus, carbamate and pyrethroid insecticides^[51]. Neonicotinoid insecticides exhibit low toxicity toward natural products and unique targeting abilities^[52], and are among the most commonly applied plant-based insecticides worldwide^[53]. These insecticides show high efficiency, broad-spectrum targeting, good root absorption, low skin and gastric toxicity and are less toxic to other organisms and the natural ecological environment^[54–56]. Neonicotinoid pesticides overcome the disadvantages of previous generations of insecticides to which cross-resistance developed easily^[57,58].

Based on the evolution of pesticide development determined by combining keyword visible contribution analysis, many scholars have examined the degradation of different types of pesticides, influence of different pesticides on soil, drug attenuation half-life, detection of heavy metals and problems associated with pesticide residues^[59–62]. Researchers have gradually shifted from studying synthetic pesticides to analyzing organic pesticides^[63–67]. Rational and full utilization

of natural products has always been the mainstream of human progress^[68]. Ecological and environmental damage caused by pesticides is related to the continuation and development of human civilization and is a core issue influencing research directions and discussion^[69–71]. Natural products will become the main types of pesticides studied^[72,73]. The raw materials of natural products have several advantages, such as their environmental protection, pollution-free and rich natural resource properties. This observation is supported by the steady increase in research on the resistance of pests to natural products.

2.1 Research related countries, cited sources and organizations analysis

For this review, we used CiteSpace 5.8.R3 and VOSviewer 1.6.18 to analyze the resistance of insects to natural products. The results showed that studies were mainly performed in Brazil, China, the USA and other countries (Fig. 2). We first set the number of citation from more than five countries, screened 73 countries that met the requirements, and calculated the total strength of citation links between these countries and other countries. Based on the keywords from bibliometrics analysis, published literature includes three aspects: plant-derived pesticides, fatality rate and natural products. The most common keyword, “plant-based insecticides”, was closely associated with “natural enemies” and “lethal”. With the transformation of synthetic pesticides such as plant-derived pesticides and increase in detailed pesticide research, researchers are increasingly focused on the development of new pesticides derived from plants and natural sources. Research on the introduction, domestication and large-scale development of plants for producing natural pesticides has been well-received. However, there is a large imbalance between relevant studies in different countries. Visual analysis showed that the top countries are the USA (20,497 citations and 598 references), China (6767 citations and 450 references), Canada (8523 citations and 107 references), Italy (4181 citations and 146 references), Brazil (4760 citations and 329 references), and India (6696 citations and 253 references). In the visual analysis diagram of citation in each country, the size of different circles represents the citation frequency, with a larger circle reflecting a higher citation frequency. Combined with the results in Fig. 2(a), both China and the USA are active in this field of research. The USA has the largest number of references, although the color is more blue, indicating that research in the USA has increased in the past few years. However, researchers in Brazil, China and Italy have recently shown great interest in this field, and the color is more orange (Fig. 2(b)). In addition, in Fig. 2(c), the research situation of

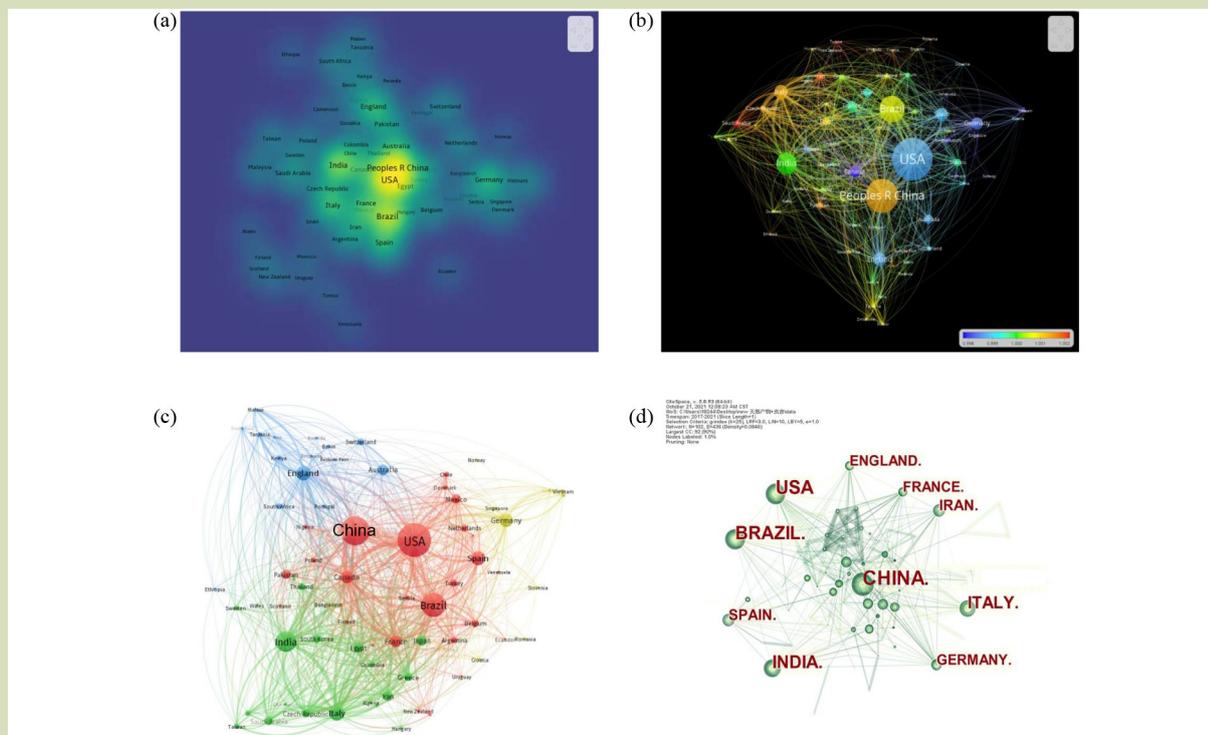


Fig. 2 Research on natural compounds in crop pest control countries (node size represents keyword intensity; links represent connections between these keywords). (a) Density of each country. Yellow and green areas represent frequent and less frequent countries, respectively; a yellow background color indicates a higher frequency of the study area. (b) Country coverage visualization. A larger number leads to a redder color, indicating that the country is closer to the forefront of research. (c) Network visualization of countries. Different colors represent different clusters, and research areas of countries covered by the same color are more similar. (d) Top ten countries. A larger value is shown as a larger circle, indicating that research in this field is more widely conducted in the corresponding country. VOSviewer1.6.18 was used for drawing images (a–c) and CiteSpace 5.8 for image (d).

each country is divided into different research areas with different colors; the research topics of each country with the same color tend to be consistent. Based on the diversity of pests, this literature survey may alert researchers in other countries to topics related to resistance to natural products. Through statistical analysis, this review focused on not only countries with a high proportion of published papers, but also countries with less research to obtain more comprehensive and valid data on insect resistance to natural products. However, there were some limitations; for example, although many research papers are added to Web of Science each day, only a small number can be compiled into the core database.

We used CiteSpace 5.8.R3 software for visual analysis of citation sources, for the period between 2017 and 2021, and keyword indices “(natural products or plant pesticides or green pesticides) and (pesticides or resistance (insects or pests))”. We set the minimum citation source threshold at 5 and 130 citation sources met the requirements out of 808 results. The top

sources in terms of total connection strength were *Pest Management Science* (2888 citations and 96 documents), *Industrial Crops and Products* (1422 citations and 64 documents), *Journal of Economic Entomology* (2188 citations and 101 documents), *Crop Protection* (2404 citations and 53 documents), *Journal of Agricultural and Food Chemistry* (2484 citations and 77 documents), and *Journal of Pest Science* (912 citations and 59 documents). As shown in Fig. 3, the results showed that there were descriptive studies, experimental series, investigation reports and research papers in the field of plant derived pesticides, which mainly focused on the species, characteristics of action and research methods of plant-derived pesticides. The top 100 most cited articles had an average of 26 citations. The most cited journal is the *Journal of Economic Entomology*, with 101 citations. As researchers give increasing attention to environmental protection pesticides, the use of synthetic pesticides has been gradually replaced. By 2021, there were more than 700 articles. Although it is speculated that synthetic pesticides, and chemical prevention and control cannot be completely replaced in the foreseeable future, the

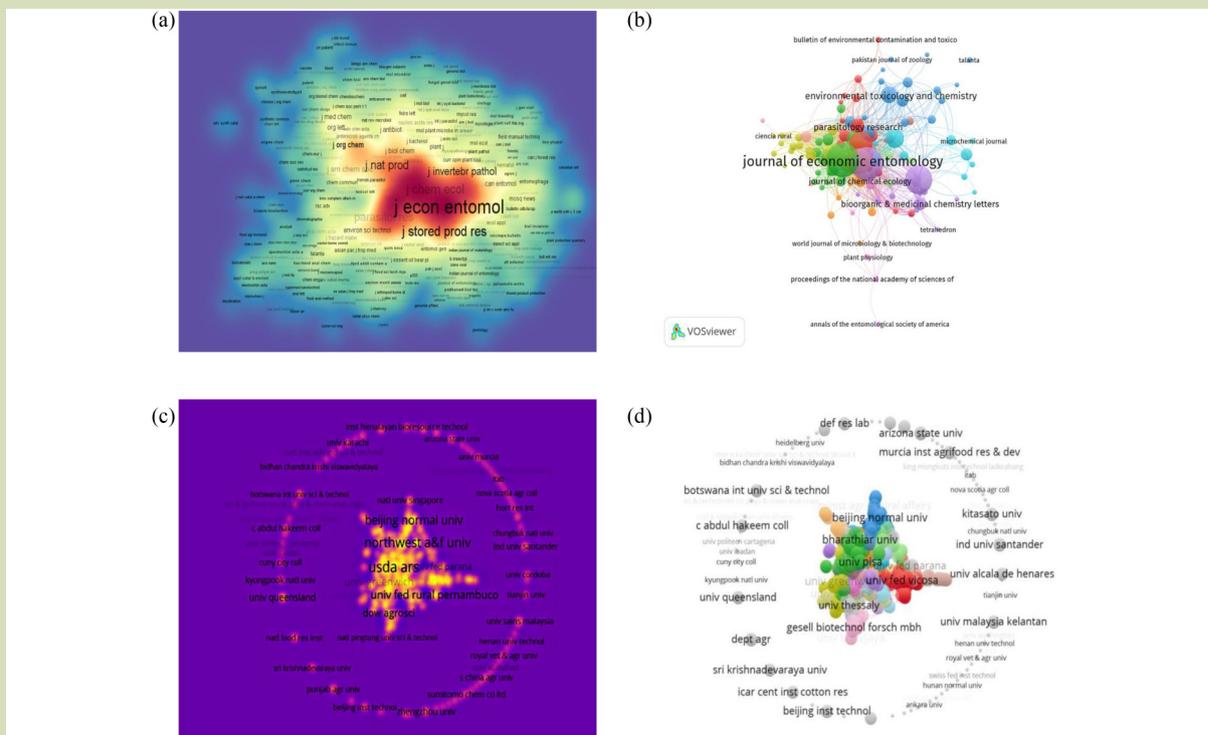


Fig. 3 Cited sources and organizations of natural compounds in crop pest control. The node size represents the strength of cited sources and organizations and the links represent the connection between these cited sources and organizations. (a) Density visualization of cited sources. The red area represents highly cited sources, and the blue area represents less cited sources. (b) Network visualization for cited sources, with different colors representing different clusters. (c) Density visualization of organizations. The yellow area represents highly cited sources, and the purple area represents less cited sources. (d) Network visualization for organizations, with different colors representing different clusters. VOSviewer 1.6.18 was used for drawing images (a–d).

development of environmental protection natural products and synthetic pesticides will be an inevitable trend.

We used VOSviewer 1.6.18 software for visual analysis of citation organizations. We set the screening conditions as follows: first, if the number of tissues in the article is greater than 25, it will be discarded if it is considered specific; secondly, if the number of citations is greater than or equal to 1, the tissues in the article will be included in the map. So we screened from 2920 organizations visualization analysis of 243 eligible organizations. Different colors in the figure indicate different clusters, and the size of the circle indicates the number of publications. The thickness of the lines represents the strength of the connections between countries. This is also consistent with the number of publications from national journals above. As shown in Fig. 3, the USDA Agricultural Research Service has published the most relevant papers and appears most prominently in the visual analysis chart. It also works with 10 other institutions, and there exists a strong link among them. Other top-ranking organizations included the

University of Pisa (1890 citations and 52 documents), the University of British Columbia (4977 citations and 23 documents), the University of Camerino (704 citations and 29 documents), the University of Greenwich (1575 citations and 24 documents) and Royal Botanical Gardens (597 citations and 19 documents). The visual analysis of each organization can help readers understand organizational cooperation in this field. It is hoped that the analysis of this aspect can be strengthened in the future.

2.2 Key research areas

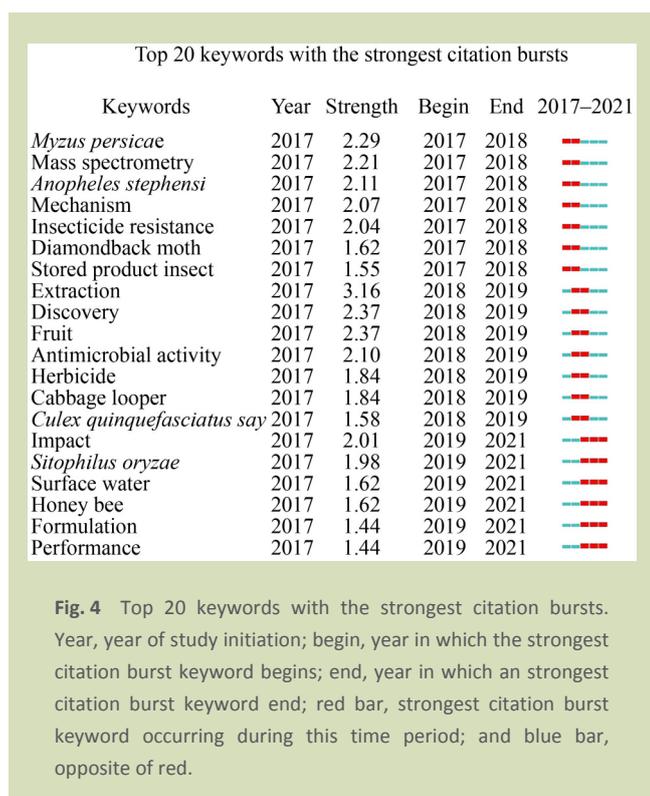
We used the emergency detection function provided by CiteSpace 5.8.R3 to rapidly identify several keywords, which can help researchers master current key research areas. Information on research frontiers can provide directions for exploring and revealing new areas. With scientific development and progress, frontier and key research areas are dynamic and rapidly evolving. According to the CiteSpace analysis, breakthrough words, such as insecticide, extract and drug

resistance, which have overlapped with high-frequency keywords since 2017, are prioritized in this review. In addition, research frontier breakthrough terms based on the data were combined with the high-frequency keywords mentioned above to summarize the prevention and control of natural product insecticides on key pests such as Noctuidae, *Plutella xylostella*, *Culex pipiens pallens*, and storage insects. The details of breakthrough words in frontier research areas are shown in Fig. 4. We combined the frontier research areas and keywords and other literature quantitative analysis to provide comprehensive evidence of natural product resistance to insect pests in this field.

3 COMPONENTS OF NATURAL PRODUCTS ACTIVE AGAINST CROP INSECT PESTS

We combined the results on insect resistance of natural products analyzed in this review (Section 2). Particularly, cluster 3 is shown as the light blue area, and its representative co-occurring words are natural product (495 occurrences), structure (197 occurrences), derivative (194 occurrences), active compound (75 occurrences) and structure-activity relationship (60 occurrences) (Fig. 1). This research area focuses on active components and structure-activity

relationships of natural products, with the aim of making structural modifications to natural products and developing derivatives with high efficiency, low toxicity and environmental safety. These efforts are essential for using natural products to control insect pests. Cluster 4 is yellow, and the main co-occurring words were essential oil (321 occurrences), oil (265 occurrences), sesquiterpene (40 occurrences), and plant essential oil (36 occurrences) (Fig. 1). Chemical insecticides affect insects; however, their application causes environmental pollution and affects human health. Natural products have long been used as insecticides, and can serve as models and inspiration for the development and synthesis of new pest control agents^[74]. Therefore, these agents may be good substitutes for synthetic pesticides. Big data has shown that it is necessary to understand the chemical classification of natural products. However, the application of different preparations in production and life is a major challenge for researchers. Exploring new environmentally friendly and pollution-free pesticides is feasible. Combined with the data from bibliometric analysis, researchers are actively studying the structural characteristics of active extracts commonly used in plant pesticides, such as alkaloids, flavonoids and terpenoids. This literature review revealed several such research articles; however, there were few comprehensive reviews based on such articles. Studies are needed to systematically organize and summarize research on the resistance of natural products to pests.



3.1 Alkaloids

Alkaloids are nitrogen-containing basic organic compounds that are common in nature and have similar basic properties. Most alkaloids have complex ring structures^[75]. Based on chemical structure, alkaloids are classified into a number of types, including piperidine, isoquinoline, indole, terpenoid, steroidal and quinoline alkaloids^[76]. These alkaloids have a wide range of biological activities as well as advantages of low toxicity, high efficiency, high selectivity and resistance to pests; consequently, they meet the requirements of ideal pesticides^[77].

Owing to the pivotal role of natural alkaloid products in the management of pests, many scholars have conducted in-depth research on them^[78–81]. Xia et al.^[82], for the first time, studied the antifeedant effects of hexahydro-benzophenanthridine alkaloids on mosquito larvae and other pests. Compounds with C-6 carbonyl or higher oxidation show stronger activity than other compounds. These compounds can be developed into preparations for controlling the larvae of *C. pipiens pallens* and *Aedes albopictus*. Seven compounds were isolated and extracted

from *Sophora alopecuroides*, among which sophocarpine and sophoridine were the most abundant. A study on the effects of these two compounds on the *Diaphorina citri* Kuwayama indicated that these two alkaloids could repel *D. citri* at high concentrations (50 and 70 mg·mL⁻¹). Also, a 50 mg·mL⁻¹ (1:1, v/v) combination of sophocarpine and sophoridine was found to have a synergistic effect and greater behavioral effects than that caused by the individual alkaloids^[83]. Eleven compounds were isolated from *Corydalis curviflora* Maxim. and their insecticidal activities studied. The compounds: curviflorain A, curviflorain B and 6-acetylambrinine were found to have promising activity against the larvae of *C. pipiens pallens* and *Aedes albopictus*. These compounds were also tested against the insect pests, *Mythimna separata* and *Schizaphis graminum*. These findings provide a better understanding of the insecticidal activity of *C. curviflora* extract and its active compounds, suggesting this extract as a potential candidate for the development of botanical pesticides^[41]. Using avermectin as a positive control, and matrine and sophocarpine as representative alkaloids, the physiologic and biochemical effects of matrine and sophocarpine in *Sophora alopecuroides* against pea aphids (*Acyrtosiphon pisum*) were determined. The aphids treated with matrine and sophocarpine developed the intoxication symptoms of convulsions, paralysis and death. However, avermectin produced no convulsions^[84].

Alkaloids have effective killing effects on common crop pests and bacteria, including *D. citri*, *C. pipiens pallens* and *A. albopictus*. Compared to synthetic pesticides, alkaloids have a superior utilization value and can be developed as novel pesticides.

3.2 Flavonoids

Flavonoids are polyphenolic secondary metabolites that occur widely in nature^[85]. Structurally, they are composed of two benzene rings, connected by an oxygen-containing heterocycle^[86]. Flavonoids have antiallergic, anticancer, antioxidant, antibacterial and antiviral properties, and are widely used as insecticides^[87-89] to control a variety of insect pests, such as *P. xylostella*, aphids, locusts and tobacco mosaic virus^[90-93].

In the past, *P. xylostella* larvae caused considerable irreversible damage to crops, fruits and vegetables. Researchers^[94-98] studied the insecticidal activity of a natural flavonoid insecticide extracted from leguminous grapevine against *P. xylostella*. The insecticide has an extensive insecticidal effect, strong contact effect, gastric toxicity and antifeedant effect on

insects. It has broad-spectrum insecticidal activity and can control more than 800 species of pests belonging to 137 families in 15 orders^[99-101]. The results showed that *Lymantria dispar* had low toxicity and a high contact effect on the third instars of the diamondback moth. The toxicity of the botanical pesticide rotenone to the third instars of *L. dispar* was determined using the drop method. The results showed that *L. dispar* had low toxicity and a high contact effect on the third instars of the diamondback moth. The median lethal concentrations (LC₅₀) at 12, 24, 36 and 48 h were 14.1, 10.4, 9.75, and 9.51 mg·L⁻¹, respectively. Also, the toxicity of *L. dispar* increased with the increase in exposure time^[102]. The effects of three flavonoids used as aphicides on woolly apple aphid and *Eriosoma lanigerum* were studied using a cut-shoot bioassay test; the three flavonoids were quercetin dehydrate, rutin hydrate and naringin, and they were tested at concentrations of: 100, 1000 and 10,000 mg·L⁻¹. The results showed that the three flavonoids had insecticidal activity against the target aphids in a concentration-dependent manner, and the mortality of the nymphs was higher than that of the adult aphids^[103]. As pests, aphids have long harmful periods of colonization and occur in large numbers in vegetable cultivation. Neochamaejasmine A is a new type of slightly toxic botanical insecticide, belonging to the flavonoids. In a field trial on the potential of 1.6% daphneantoxin emulsion in water to control vegetable aphids, this compound was found to control of more than 80%, at 10 d after treatment, indicating that it can be effectively used as a botanical insecticide^[104].

The broad-spectrum insecticidal activity of some flavonoids has been verified using field experiments, which can better explain the anti-insect properties of flavonoids. The locust plague is a global problem that often leads to serious economic losses and food shortages^[105]. Flavonoids also possess a high insecticidal activity on locusts and hence have a great application.

3.3 Terpenoids

Terpenoids are a group of chemical compounds containing various substances and occur widely in nature^[106]. They are volatile compounds released by the host plants^[107] and are composed of isoprene units usually classified as monoterpenes, sesquiterpenes, diterpenes, triterpenes and tetraterpenes according to the number of their connecting monomers^[108]. Terpenoids have a wide range of biological activities^[109,110] and are widely used in spices, medicines, pesticides and industrial compounds^[111].

Laurinterol is a cyclolaurane-type halogenated sesquiterpene, which is the main secondary metabolite in the acetic acid-ethyl ester extract of the red algae, *Laurencia nidifica*^[112]. Ishii et al.^[113] for the first time reported its repelling activity on *Sitophilus zeamais*, insecticidal activity on *Reticulitermes speratus*, acetylcholinesterase inhibitory activity and toxicity to *Artemia salina*. The findings suggest that *L. nidifica* may be a good source of bioactive natural products with insecticidal activity. However, the chemical transformation and structure-activity relationship of lauryl alcohol needs further study. The main active constituents of the insecticide obtained from *Rhododendron molle* is tetracyclic diterpenes with rhodojaponin-III one of the more active components^[114,115]. A pot experiment testing the efficacy of rhodojaponin-III against *Spodoptera litura* larvae showed that after treatment with a concentration of 500 g·mL⁻¹ rhodojaponin-III, the population reduction rate of *S. litura* was 53.2%, 64.1%, and 79.7% at 1, 3 and 7 days after treatment, respectively. The leaf protection rates 5 and 10 days after treatment were 63.6% and 68.2%, respectively, and the effect was superior to that of toosendanin (250 g·mL⁻¹)^[116].

The insecticidal activity of terpenoids has been widely confirmed. Terpenoids have a good insecticidal activity which is different from other pesticides acting on specific pests. They act against a variety of highly damaging pests and hence, could have a key role in agriculture.

3.4 Phenylpropanoids

Phenylpropanoid compounds, which are chemical components with one or more central C6–C3 units^[117], occur widely in nature and can be obtained from a variety of plant food sources, such as potatoes^[118] and cabbage^[119]. These compounds are widely used in food, medicine and agriculture, and have extensive research value^[77].

Asaricin, isoasarone and trans-asarone were isolated from the hexane extract of the roots of *Piper sarmentosum*. These three compounds are insecticidal being acetylcholinase inhibitors. Its lethal mechanism is the inhibition of acetylcholinase directly affects bradycardia, bronchoconstriction and prolonged muscle contraction in insects^[120]. Seven phenylpropanoid compounds were isolated from ethyl acetate extract of *Alpinia galanga* rhizomes, and their insecticidal activities were tested. 1'S-1'-acetoxychavicol acetate was identified as the most prominent insecticidal compound. The LC₅₀ after 24 and 48 h of treatment were 1.63 and 1.40 µg per larva, respectively. These two active compounds decreased glutathione S-transferase activity and increased the acetylcholinesterase

activity^[121]. *Lycoriella ingenua* and *Coboldia fuscipes* are two of the most economically important insect pests of cultivated mushrooms. The toxicities of the three phenylpropanoids (methyleugenol, myristicin and safrole) derived from the aerial parts of *Asarum sieboldii* (Aristolochiaceae) exhibited toxicity toward fly larvae. In a contact fumigant mortality bioassay with *L. ingenua* and *C. fuscipes* larvae, methyleugenol (1.46 and 2.33 g·cm⁻²) was the most toxic compound, based on 24-h LC₅₀^[122]. Methyleugenol is expected to become a commercial insecticide for protecting cultivated mushrooms. A pure natural product was obtained from the root powder of *Stellera chamaejasme*, which was identified as 7-hydroxycoumarin. Laboratory bioassays showed that this compound had good insecticidal activity against *Aphis craccivora* and *C. pipiens pallens* with 24-h LC₅₀ of 19.6 and 0.44 mg·L⁻¹, respectively, and is expected to developed as a new commercial insecticide^[123]. Podophyllotox-one and desoxy-podophyllotoxin are two lignans isolated from *Sinopodophyllum hexandrum*. When the concentration of podophyllotox-one was 50 µg·mL⁻¹, the mortality of *A. aegypti* larvae reached 73%. The effect of desoxy-podophyllotoxin was more obvious; treating larvae with a concentration of 10 µg·mL⁻¹ for 8 days resulted in 100% mortality, which is more effective than the commercial insecticide diflubenzuron^[124].

Here, we describe the role of phenylpropane compounds as insecticidal agents, and some of them have the advantages of being non-toxic, efficient, with a stronger pest control effect compared to commercial insecticides. In future research, will be needed to further determine the non-target toxicity of these natural products to allow their development as commercial natural-product pesticides.

3.5 Benzoxazinoids

In contrast to the natural products described above, benzoxazines (BXs) are a class of defense-related secondary metabolites widely found in the Gramineae^[125]. It is mainly divided into two categories: benzoxazinone and benzoxazolinone^[126]. These substances exist in different forms in different tissues of plants, participate in various defense responses in plants, and help plants resist biotic and abiotic stresses^[127]. A increasing number of studies have shown that BXs have a wide range of antifeedant, insecticidal, antibacterial and allelopathic activities^[128]. The activities of these compounds against insects are describe below.

To determine whether BXs in maize are inhibit aphids, Ahmad et al.^[129] studied the differences between BX-deficient and

BX-producing maize lines. It was found that BX-deficient maize was more susceptible to aphids and BX-producing maize had an effective defense against *Rhopalosiphum padi*. Glauser et al.^[130] combined their studies with metabonomics techniques and showed that BXs was effective against generalist *Spodoptera littoralis* and the specialist *Spodoptera frugiperda*. Meihls et al.^[131] also demonstrated the anti-aphid activity of BXs. Wheat seedlings are frequently affected by herbivorous pests. To reduce the harm due to pesticidal activity and maintain the growth of plants, they have evolved various defense mechanisms. Batyrshina et al.^[132] combined transcriptology, metabonomics and physiology to better understand the differences in wheat defense mechanisms and found that BXs had better defense efficacy against aphids. In addition, 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (DIMBOA) and DIMBOA-glycoside (DIMBOA-Glc) are important BXs with insecticidal activity^[133,134]. However, little is known about how their biosynthesis is regulated. Zhang et al.^[135] found that ZmMPK6 can be rapidly activated by wounding and simulated herbivory. Silencing ZmMPK6 in maize decreased ethylene levels induced by simulated herbivores and ZmMPK6-silenced plants exhibited elevated DIMBOA/DIMBOA-GLC and insect resistance. It is known that ZmMPK6 and ethylene pathway are inhibitors of DIMBOA/DIMBOA-GLC, and the insect resistance activity of BXs can be enhanced by regulating these two pathways. As mentioned above, BXs produced in maize and wheat can prevent and control pests, but some pests are tolerant to BXs, and its mechanism is not clear. Based on these results, further research found that 6-methoxy-2-benzoxazolinone (MBOA), the decomposed product of BX, can be a precursor to 3- β -D-glucopyranosyl-6-methoxy-2-benzoxazolinone (MBOA-N-Glc) in the intestine of *S. littoralis* and *S. frugiperda* caterpillars, but not in European corn borer, *Ostrinia nubilalis*. Subsequent studies found that the presence of MBOA had no effect on the growth of *S. littoralis* and *S. frugiperda* caterpillars, but inhibited the growth of *O. nubilalis*. It has been suggested that the glycosylation of MBOA is an important detoxification mechanism to help insects tolerate corn BXs; and the potential for novel insecticides that prevent the glycosylation of MBOA should be investigate^[136]. In addition, plants can change the composition and structure of the soil, thus changing the growth of the next generation of plants. This process is called plant–soil feedback^[137]. Understanding plant defense mechanisms against insects through this process has gain recent interest. Many studies have found that maize can regulate the surrounding soil by secreting root exudates including BXs, and the soil microflora secreting BXs can improve the insect resistance of plants^[138,139]. These natural products are mostly responsible for insect-resistance in

Gramineae plants, and their in-depth study will help to greatly reduce the crop loss caused by pests.

These studies show that many natural products provide insect-resistance in plants. These natural products widely occur in nature, meet the green-pesticide requirements and have great research value. Natural products with pesticidal activity are presented in Table 1 and Fig. 5.

4 MODE OF ACTION NATURAL PRODUCTS AGAINST PESTS

In practical application of natural products against insect pests, the purple cluster 5 of keywords identified in bibliometrics analysis was key with co-occurring terms: PPM (143 occurrences), plant extract (92 occurrences), larvicidal activity (80 occurrences), LC₅₀ (74 occurrences) and lethal concentration (52 occurrences) (Fig. 1). These insecticidal indicators are critical in the natural product insecticidal chain, and the level of indicators intuitively indicates the strength of their association with natural product use in pest management. To exert insecticidal effects on harmful pests, natural products must first enter the insect in a specific manner to reach the action site, and then function in this target area. The entry mechanism into the pest body and transport the action site can be considered as the mode of action of natural products against pests, several of which are described below.

4.1 Gastrointestinal toxicity

Chemicals enter the body through the mouthparts and digestive system of pests, causing poisoning or death, and some natural products have this gastrointestinal toxic effect. The gastrointestinal toxicity of tea saponins to the second instar *Ectropis obliqua* larvae was determined in a leaf dipping bioassay. Thirty *E. obliqua* larvae were starved for 24 h and transferred to a glass Petri dish (each Petri dish contained two leaves soaked in tea saponin solution). The tea saponins were strongly gastrointestinal toxic (LC₅₀ of 22.4 mg·L⁻¹). In-depth analysis of the mechanism revealed that after consuming the tea saponins, the intestinal villi were shortened, intestinal wall cavity was destroyed and larvae died^[164]. The gastrointestinal toxic activities of eucalyptus essential oil, *Baeckea frutescens* essential oil, *Brucea javanica* and matrine against *Helicoverpa armigera* were determined using the feeding weighing method. Four types of natural products were added to artificial feed, to which one-third instar starved for 4 h were added. The gastrointestinal toxicity of eucalyptus essential oil and *B. javanica* was high among the four natural products, leading

Table 1 Natural products with anti-crop insect pests activities

Natural product	Compound name	Source	Control target	Insecticidal activity	Positive control	Insecticidal activity	Reference	
1	Terpenoids	Azadirachtin	<i>Azadirachta indica</i> A. Juss.	<i>Tirathaba rufivena</i>	LC ₅₀ 28.8 mg·L ⁻¹	–	–	[140]
2		Rhodojaponin-III	<i>Rhododendron molle</i>	<i>Spodoptera litura</i>	LC ₅₀ 125 µg·mL ⁻¹	Toosendanin	LC ₅₀ 250 µg·mL ⁻¹	[116]
3		Laurinterol	<i>Laurencia nidifica</i>	<i>Reticulitermes speratus</i>	LD ₅₀ 2.20 µg per insect	Rotenone	LD ₅₀ 0.11 µg per insect	[113]
4		Curcuphenol	<i>Didiscus oxeaata</i>	<i>Spodoptera littoralis</i>	EC ₅₀ 15.8 µg·cm ⁻²	Thymol	EC ₅₀ 23.9 µg·cm ⁻²	[141]
5		10-Hydroxy-11-methoxy-dihydrocurcuphenol			EC ₅₀ 15.8 µg·cm ⁻²			
6		Hydroxycolorenone	<i>Nephthea chabrolii</i>	<i>Spodoptera littoralis</i>	LC ₅₀ 8.8 mg·L ⁻¹	–	–	[142]
7		Methoxycolorenone			LC ₅₀ 15.6 mg·L ⁻¹	–	–	
8		Chabrolene	<i>Coral nephthea</i>	<i>Sitophilus zeamais</i>	EC ₅₀ 12.5 µg·cm ⁻²	–	–	[143]
9		3,4-Dihydroxybenzoic acid	<i>Holothuria atra</i>	<i>Spodoptera litura</i>	LC ₅₀ 6.01 mg·mL ⁻¹	–	–	[144]
10		4-Hydroxy-3-methoxy-benzaldehyde			LC ₅₀ 17.01 mg·mL ⁻¹	–	–	
11		Sporyzin A	<i>Aspergillus oryzae</i>	<i>Artemia salina</i>	61.9% mortality at 100 mg·L ⁻¹	Huperzine A	98% mortality	[145]
12		Sporyzin B			42.9% mortality at 100 mg·L ⁻¹			
13		Sporyzin C			32.8% mortality at 100 mg·L ⁻¹			
14		JBIR-03			74.2% mortality at 100 mg·L ⁻¹			
15		Emindole SB			60.3% mortality at 100 mg·L ⁻¹			
16		Emeniveol			31.4% mortality at 100 mg·L ⁻¹			
17	Alkaloids	Coclaurine	<i>Discaria chacaye</i>	<i>Drosophila melanogaster</i>	LD ₅₀ 78.2 µg·mL ⁻¹	–	–	[146]
18		Boldine	<i>Talguenea quinquenervia</i>		LD ₅₀ 70.8 µg·mL ⁻¹	–	–	
19		Pukateine	<i>Peumus boldus</i>		LD ₅₀ 70.9 µg·mL ⁻¹	–	–	
20		Sophocarpine	<i>Sophora alopecuroides</i>	ACP	50 mg·mL ⁻¹	N,N-Diethyl-met-toluamide	30 mg·mL ⁻¹	[83]
21		Sophoridine			70 mg·mL ⁻¹			
22		Curviflorain A	<i>Corydalis curviflora</i> Maxim.	<i>Culex pipiens pallens</i> , <i>Aedes albopictus</i>	LC ₅₀ 15.9 µg·mL ⁻¹ , LC ₅₀ 8.42 µg·mL ⁻¹	Pyrethrin	LC ₅₀ 4.36 µg·mL ⁻¹ , LC ₅₀ 3.54 µg·mL ⁻¹	[82]
23		Curviflorain B			LC ₅₀ 16.1 µg·mL ⁻¹ , LC ₅₀ 15.5 µg·mL ⁻¹			
24		Ambiguanine A			LC ₅₀ 50.1 µg·mL ⁻¹ , LC ₅₀ 86.0 µg·mL ⁻¹			
25		1,1-Dimethyl-6-methoxy-7-hydroxyl-1,2,3,4-tetrahydroisoquinoline			LC ₅₀ 52.1 µg·mL ⁻¹ , LC ₅₀ 76.9 µg·mL ⁻¹			
26		Hendersine B			LC ₅₀ 23.3 µg·mL ⁻¹ , LC ₅₀ 31.0 µg·mL ⁻¹			

(Continued)

Natural product	Compound name	Source	Control target	Insecticidal activity	Positive control	Insecticidal activity	Reference
27	Coryximine			LC ₅₀ 54.29 µg·mL ⁻¹ , LC ₅₀ 94.3 µg·mL ⁻¹			
28	Isochotensine			LC ₅₀ 92.4 µg·mL ⁻¹ , LC ₅₀ 99.8 µg·mL ⁻¹			
29	Bruceine D	<i>Brucea Javanica</i> (L.) Merr.	<i>Plutella xylostella</i> , <i>Spodoptera exigua</i> Hübner, <i>Spodoptera litura</i> Fabricius	Antifeedant effects 93.8%	Azadirachtin	Antifeedant effects 22.6%	[84]
30	Anisodine	<i>Anisodus tanguticus</i> (Maxim.) Pascher	<i>Brevicoryne brassicae</i>	LC ₅₀ 3.16 mg·mL ⁻¹	Rotenone	LC ₅₀ 0.400 mg·mL ⁻¹	[147]
31			<i>Rhopalosiphum padi</i>	LC ₅₀ 3.67 mg·mL ⁻¹		LC ₅₀ 1.18 mg·mL ⁻¹	
32			<i>Myzus persicae</i>	LC ₅₀ 4.16 mg·mL ⁻¹		LC ₅₀ 0.566 mg·mL ⁻¹	
33			<i>Aphis craccivora</i>	LC ₅₀ 0.495 mg·mL ⁻¹		LC ₅₀ 0.617 mg·mL ⁻¹	
34			<i>Aphis gossypii</i>	LC ₅₀ 0.429 mg·mL ⁻¹		LC ₅₀ 0.436 mg·mL ⁻¹	
35			<i>Sitobion miscanthi</i>	LC ₅₀ 0.881 mg·mL ⁻¹		LC ₅₀ 1.03 mg·mL ⁻¹	
36	Anisodamine		<i>Brevicoryne brassicae</i>	LC ₅₀ 1.32 mg·mL ⁻¹		LC ₅₀ 0.400 mg·mL ⁻¹	
37			<i>Rhopalosiphum padi</i>	LC ₅₀ 1.64 mg·mL ⁻¹		LC ₅₀ 1.18 mg·mL ⁻¹	
38			<i>Myzus persicae</i>	LC ₅₀ 0.846 mg·mL ⁻¹		LC ₅₀ 0.566 mg·mL ⁻¹	
39			<i>Aphis craccivora</i>	LC ₅₀ 1.95 mg·mL ⁻¹		LC ₅₀ 0.617 mg·mL ⁻¹	
40			<i>Aphis gossypii</i>	LC ₅₀ 0.404 mg·mL ⁻¹		LC ₅₀ 0.436 mg·mL ⁻¹	
41			<i>Sitobion miscanthi</i>	LC ₅₀ 1.164 mg·mL ⁻¹		LC ₅₀ 1.030 mg·mL ⁻¹	
42	Aloperine	<i>Sophora alopecuroides</i>	<i>Bursaphelenchus xylophilus</i>	Inhibition of reproduction 100%	-	-	[148]
43	Caulerpin	<i>Caulerpa racemosa</i>	<i>Culex pipiens</i>	LC ₅₀ 0.86 mg·L ⁻¹	Malathion	LC ₅₀ 1.00 mg·L ⁻¹	[149]
44	Caulerpinic acid			LC ₅₀ 1.69 mg·L ⁻¹			
45	Hymenialdisine	<i>Axinella carteri</i>	<i>Spodoptera littoralis</i>	LD ₅₀ 88 mg·L ⁻¹	Precocene II	LD ₅₀ 275 mg·L ⁻¹	[150]
46	Debromohymenialdisine			LD ₅₀ 125 mg·L ⁻¹			
47	Manzamine A	<i>Xestospongia ashmorica</i>	<i>Spodoptera littoralis</i>	ED ₅₀ 35 mg·L ⁻¹	-	-	[151]
48	Amphitoxin	<i>Amphimedon compressa</i>	<i>Cylas formicarius</i>	30% mortality at 1.2 mg·L ⁻¹	-	-	[152]
49	Gelastatin A	<i>Cymbastela</i> sp.	<i>Spodoptera exigua</i>	LC ₅₀ 20.3 mg·L ⁻¹	Javelin WG	LC ₅₀ 12 mg·L ⁻¹	[153]
50	Gelastatin C			LC ₅₀ 200 mg·L ⁻¹			
51	Swinhoeiamide A	<i>Theonella swinhoei</i>	<i>Spodoptera littoralis</i>	LC ₅₀ 2.98 mg·L ⁻¹	-	-	[154]
52	Nortopsentin A	<i>Spongosorites ruetzleri</i>	<i>Culex pipiens pallens</i>	100% mortality at 10 mg·L ⁻¹	Rotenone	100% mortality	[155]
53	Nortopsentin B			100% mortality at 10 mg·L ⁻¹			
54	Nortopsentin C			70% mortality at 10 mg·L ⁻¹			
55	Nortopsentin D			40% mortality at 10 mg·L ⁻¹			

(Continued)

Natural product	Compound name	Source	Control target	Insecticidal activity	Positive control	Insecticidal activity	Reference
56	Altemicidin	<i>Streptomyces sioyaensis</i>	<i>Artemia salina</i>	LC ₅₀ 3 mg·L ⁻¹	Polynactin	LC ₅₀ 4 mg·L ⁻¹	[115]
57	Communesin B	<i>Penicillium</i> sp.	<i>Bombyx mori</i>	LD ₅₀ 5 µg·g ⁻¹	–	–	[156]
58	Communesin E			LD ₅₀ 80 µg·g ⁻¹	–	–	
59	Cristatumin B	<i>Eurotium cristatum</i>	<i>Artemia salina</i>	LD ₅₀ 74.4 µg·g ⁻¹	–	–	[157]
60	Isoechinulin A	EN220		LD ₅₀ 16.9 µg·g ⁻¹	–	–	
61	Variecolorin G			LD ₅₀ 42.6 µg·g ⁻¹	–	–	
62	Cyclopentanepropanoic acid, 3,5-bis(acetyloxy)-2-(3-(methoxyimino)octyl), methyl ester	<i>Streptomyces-VITSTK7</i> sp.	<i>Culex quinquefasciatus</i>	LC ₅₀ 430.06 mg·L ⁻¹	–	–	[158]
63	5-Azidomethyl-3-(2-ethoxy carbonyl-ethyl)-4-ethoxycarbonylmethyl-1H-pyrrole-2-carboxylic acid, ethyl ester			LC ₅₀ 881.59 mg·L ⁻¹	–	–	
64	Chloramphenicol D1	<i>Acromonium vitellinum</i>	<i>Helicoverpa armigera</i>	LC ₅₀ 930 mg·L ⁻¹	Matrine	LC ₅₀ 240 mg·L ⁻¹	[159]
65	Chloramphenicol D2			LC ₅₀ 560 mg·L ⁻¹			
66	Chloramphenicol D3			LC ₅₀ 910 mg·L ⁻¹			
67	Okalaminei B	<i>Aspergillus</i> sp.	<i>Spodoptera exigua</i>	LD ₅₀ 0.2 µg·g ⁻¹	–	–	[160]
68	Flavonoids	Rotenone	<i>Derris trifoliata</i> Lour.	LC ₅₀ 9.51 mg·L ⁻¹	–	–	[102]
69		Quercetin dihydrate	Rice	Mortality at 85.00%	Imidacloprid	Mortality at 88.3%	[103]
70		Naringin	<i>Eriosoma lanigerum</i>	Mortality at 86.7%			
71		Rutin hydrate		Mortality at 93.3%			
72		Neochamaejasmine A	<i>Stellera chamaejasme</i>	Rate of population decline 74.1%	Imidacloprid	Rate of population decline 71.1%	[104]
73		Quercetin	<i>Hypericum ascyron</i>	Survival rate 42.3%	–	–	[140]
74	Others	Curcumin	<i>Curcuma longa</i>	LC ₅₀ 3060 mg·L ⁻¹	Spirodiclofen	LC ₅₀ 661 mg·L ⁻¹	[161]
75		Matrine	<i>Sophora flavescens</i>	EC ₅₀ 238 µg·mL ⁻¹			
76		Emodin	<i>Cassia nigricans</i>	LC ₈₅ 50 µg·mL ⁻¹	–	–	[162]
77			<i>Bemisia tabaci</i>	LC ₈₅ 25 µg·mL ⁻¹	–	–	
78		Penicixanthenes A	<i>Ceriops tagal</i>	LC ₅₀ 38.5 µg·mL ⁻¹	Azadirachtin	LC ₅₀ 8.8 µg·mL ⁻¹	[163]
79		Penicixanthenes B	<i>Culex quinquefasciatus</i>	LC ₅₀ 80 µg·mL ⁻¹			
80		Penicixanthenes C		LC ₅₀ 11.6 µg·mL ⁻¹			
81		Penicixanthenes D		LC ₅₀ 23.5 µg·mL ⁻¹			

Note: LD₅₀, median lethal dose; EC₅₀, concentration for 50% of maximal effect; ED₅₀, 50% effective dose. “–” means there is no positive control added in the experiment.

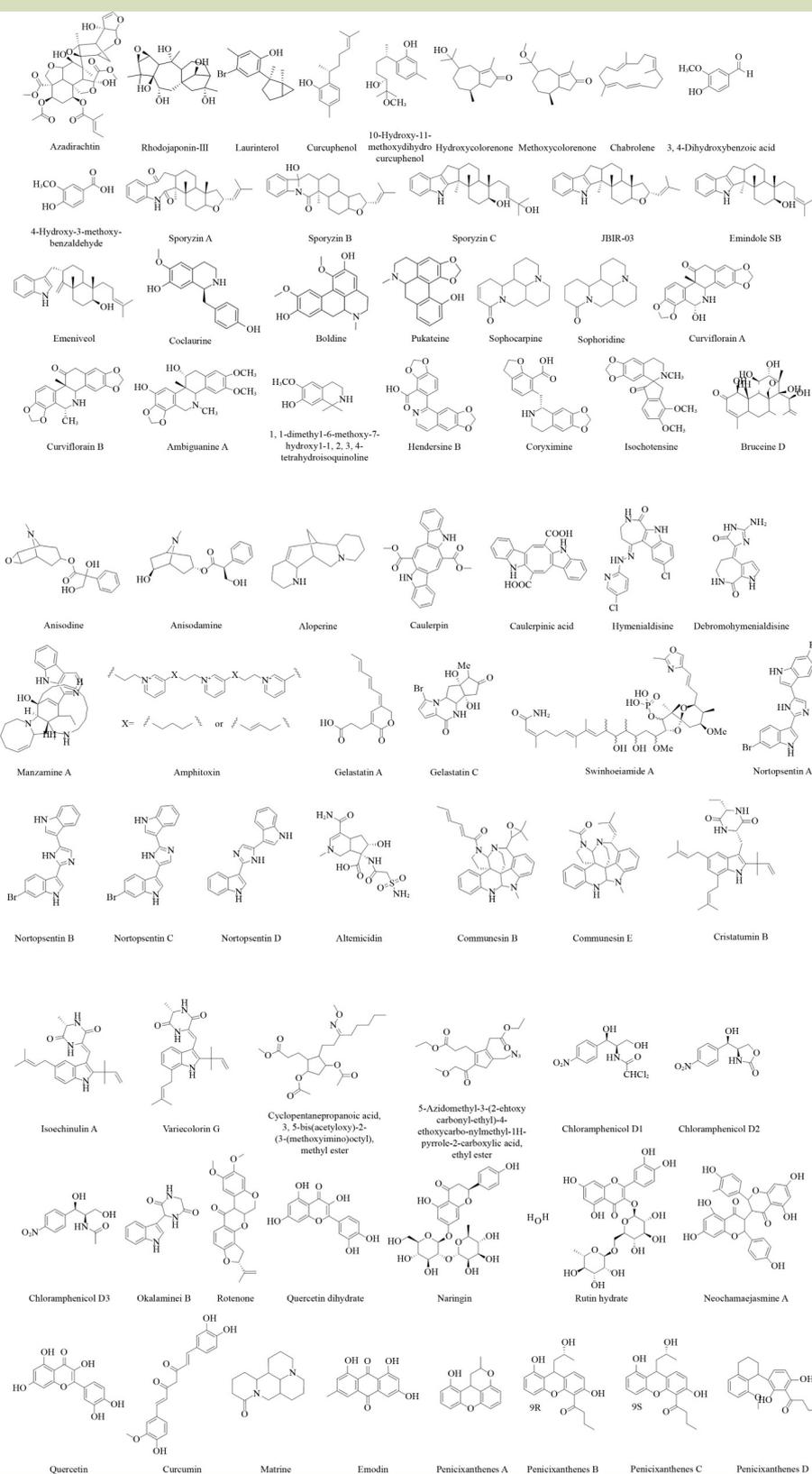


Fig. 5 Natural products with anti-crop insect pests activities.

to more than 10% mortality^[165]. Study showed that toosendanin, a triterpenoid in neem and *Melia azedarach*, has a strong gastrotoxic effect on *Pieris rapae*^[166]. Currently, spinosine is internationally recognized as the biological pesticide with the highest biological activity; spinosine also has low non-target toxicity, a wide insecticidal range in pests, and is environmentally friendly. Spinosine exerts gastrointestinal toxic effects on nocturnal moth, mosquitoes and flies^[167].

4.2 Contact toxicity

Some natural products enter the body through the epidermis of pests and can be lethal to pests. This mode of action is called a contact insecticidal effect, referred to as contact toxicity. The contact activity of *Litsea cubeba* essential oil against *Drosophila* was evaluated following direct contact between larvae and filter paper soaked in the essential oil. The contact effect was determined from the contact time and concentration of essential oil. The mortality of larvae was positively correlated with the concentration of essential oil. After contact with 1 $\mu\text{L}\cdot\text{cm}^{-2}$ essential oil, the mortality was about 90%^[168]. Liang et al.^[169] found that the essential oil of *Rhododendron thymifolium* can kill adults of *Tribolium castaneum*. In addition, the extract of *R. thymifolium* strongly inhibits acetylcholinesterase. Research on mixed use of pesticides has made numerous advances. Mixing different plant products can enhance their efficacy, and can also reduce the development of resistance in target insects^[170]. Kumar et al.^[171] reported that rotenone, a widely used botanical pesticide, has a strong contact effect on pests in contact tests on isovitexin and vitexin extracted from bamboo. Four compounds, lupeol, stigmaterol, stigmast-7-en-3-ol, and labdane diterpene, were isolated from *Dodonaea viscosa* Jacq. These four compounds showed different degrees of insect-resistant activity against crop pests^[172].

4.3 Antifeedant activity

After being consumed by insect pests, some natural products disrupt its normal physiologic functions suppressing its appetite and it can no longer eat and will starve to death. Data shows that hexahydro-benzophenanthridine alkaloids exhibit great potential as anti-dopaminergic in treating the disease associated with the central nervous system, which can generate antifeeding reactions in insects^[173,174]. A range of concentrations of bruceine D were added to the feed of diamondback moth as freshly molted third instars (each group of 100) in insect feeding containers. After 3 h of hunger, excess food was provided. When the larvae were exposed to 100 $\mu\text{g}\cdot\text{mL}^{-1}$ bruceine D for 24 and 48 h, antifeeding effects of

94% and 97% were observed, which were significantly greater than that of azadirachtin^[175]. Catnip oil also shows a useful antifeedant effect, with more than 85% *Haematobia irritans* not feeding when exposed to catnip oil doses of 0.2 or 2 mg^[176]. The main reason why insects refuse to eat is that chemical refusals inhibit the function of insect taste chemosensors and make them unable to recognize food normally^[177]. However, research on the active ingredients of insect antifeedants and impact of environmental activities on non-target organisms require further investigation.

4.4 Growth inhibition

Inhibiting the growth of insect pests is also one of the main ways of natural products can be used to control insect pests. The growth rate of fresh weight of the third instars treated with *L. dispar* solution was lower than that of distilled water and DMSO solution treatment for 3 consecutive days, indicating that *L. dispar* could inhibit the growth of diamondback moth larvae^[61]. Azadirachtin is the main insecticidal component in neem tree, and it belongs to the tetranortriterpenoids^[178,179]. Research confirmed that azadirachtin inhibited insect eggs from hatching and also affected the newborn larvae of treated eggs. Also, azadirachtin affected the hatching and development of larvae, pupal stage and the life span of *Tirathaba rufivena* ladybird until it reached adulthood. Therefore, it is reasonable to speculate that azadirachtin can effectively inhibit *T. rufivena* directly by being acutely toxic to its larvae and indirectly by delaying their growth and development^[140]. The effects of quercetin on the growth and development of *Calliptamus abbreviatus* have been studied. After the *C. abbreviatus* was treated with different concentrations of quercetin, the survival rate and growth rate decreased significantly, indicating that quercetin has a certain inhibitory effect on the growth of this short-winged locust, suggesting that it can be used as a locust control pesticide^[180].

Understanding the mode of action of natural products against insect pests can help to select targeted insecticides according to the physiologic characteristics and ecological habits of pests, effectively control their harm and control their density at the level of insufficient harm.

5 MECHANISMS OF ACTION OF NATURAL PRODUCTS AGAINST CROP PESTS

From the results of bibliometric analysis, the cluster 6 keywords are shown in the dark blue area and mainly

demonstrate the importance of studying the insecticidal mechanism of natural products. The highlighted keywords include gene (167 occurrences), pathway (127 occurrences), enzyme (115 occurrences), function (91 occurrences), inhibitor (85 occurrences), toxic (62 occurrences), biology (60 occurrences), molecule (51 occurrences), and specificity (40 occurrences) (Fig. 1). Active substances from natural products can interfere with the normal life cycle of insects by affecting their hormone metabolism. For example, rotenone can bind to calcium channel proteins in the insect troponin membranes and cause rapid insect cell death by incorporating large numbers of ions into muscle cells^[21]. Previous studies demonstrated the insecticidal mechanism and provided a basis for developing additional natural product insecticides. The results of visualization analysis showed that scholars are attempting to understand pest control by studying the insecticidal mechanism, gene expression, and enzyme activity of natural products in pesticides. However, the detailed insecticidal mechanisms require further investigation.

5.1 Effects of enzymes

5.1.1 Mixed function oxidase and antioxidation prevent system enzyme system

Mixed function oxidase, also known as multifunctional oxidase or monooxygenase, is found mostly in insect livers, with small amounts also present in other tissues. Mixed function oxidase is a general term for an enzyme system and does not represent one specific enzyme^[181]. Important antioxidant enzymes in insects include superoxide dismutase (SOD), peroxidase (POD), catalase (CAT), and glutathione reductase^[182]. SOD is present in many subcells and provides the first line of defense against oxidative stress^[183]. CAT also is important for resisting external stimuli and is a key antioxidant in the development of systemic acquired resistance^[184]. POD is often oxidized by H₂O₂ to catalyze a variety of substrates^[185]. The concentration of glutathione reductase increases with increasing glutathione levels to help improve stress tolerance^[14]. To determine the effect of mulberry active substance 1-DNJ on the activity of protective enzymes in *S. exigua* larvae, the fourth instar *S. exigua* larvae were fed cabbage leaflets soaked in different concentrations of 1-DNJ for 30 s. The results showed that 1-DNJ significantly affected the activity of protective enzymes in *S. exigua*, in which the activities of SOD and CAT were first increased and then decreased, and the activity of CAT decreased significantly compared with those in the control^[186]. Additionally, eucalyptus and clove oils have been shown to have insecticidal activity against *C. pipiens pallens*, and their effects on POD, SOD, and CAT are concentration-dependent.

These oils can be used as green insecticides to control *C. pipiens pallens*^[187]. *Acrobasis advenella* is a common pest in the blackberry industry, and the effects of *Satureja hortensis* essential oil, and the main component carvacrol, were tested on *A. advenella*. The results showed that both agents caused high mortality in *A. advenella* larvae. Also, carvacrol can increase the activity of CAT in *A. advenella*^[188].

5.1.2 Acetyl cholinesterase and glutamate decarboxylase

As acetyl cholinesterase (AChE) is the main transmitter of insect sensory neurons and the excitatory synapses of the central nervous system, in insects, the ACE-1 and ACE-2 AChE genes have a high expression capacity; consequently, many insecticides are based on the inhibitory capacity of AChE as one of the effectiveness criteria^[166]. Bandara et al.^[189] found that piperidine alkaloids contained in the stem bark of *A. aegypti* inhibited the growth and development of second instar of *A. aegypti* at a high concentration, rendering the larvae incapable of entering the next stage of growth. Using chlorpyrifos as a positive control, AChE activity in adults of *Paederus fuscipes* was studied *in vivo* and *in vitro* by fumigation. The results showed that different times and doses *in vivo* had certain toxic effects on *P. fuscipes* of different sexes at 3 µL wintergreen oil. The AChE activity in the male and female adults treated with oil was significantly lower than those treated with 10 mg·L⁻¹ chlorpyrifos. Therefore, the insecticidal mechanism of wintergreen oil is probably a result of the inhibition of AChE activity, which produces the insecticidal effect^[190]. AChE is an important target for insect resistance by affecting the nervous system^[191].

Glutamate decarboxylase (GAD) involuntarily promotes synaptic formation in motor neurons by organizing glutamate receptors on the postsynaptic membrane, that is, by regulating the extracellular aggregation of glutamate neurotransmitters. To restore normal activity and function in insects, it is important to ensure the balance of GAD activity in neurons or tissues^[29]. Studies have shown that if the GAD concentration of mutant insects decreases, then the extracellular glutamate concentration will increase accordingly. A glutamate receptor antagonist was used to test TDP-43 deletion in *Drosophila melanogaster*. The results showed that GAD can promote synaptic formation and prevent excitotoxicity^[31]. Liu et al.^[30] found that the competitive antagonist of the ionic GABA receptor (GABAR) has insecticidal activity. These researchers synthesized a series of 4-aryl-5-carbamoyl-3-isoxazolols and found that they showed good antagonism against GABARs of insects such as the housefly and common cutworm and killed insect pests by affecting their nervous systems.

5.1.3 Alanine aminotransferase and chitin synthase

Essential oils (EO) can have pharmacological effects such as egg killing and insecticidal activity. It has been found that EO and as a nano emulsion (NE) may change the aspartate aminotransferase (AST), alanine aminotransferase (ALT), and glucose contents in insects^[13,15,166]. The activity of AST and ALT is used as an index to judge whether the function of the fat body in insects is normal or not. In general, as insects continue to grow, the activity of AST and ALT gradually increases^[11]. Once insects are disturbed by pesticides, the activity of enzymes such as AST and ALT will decrease^[22]. Some studies have used aniseed (*Pimpinella anisum*) EO and NE to kill the red flour beetle *Tribolium castaneum* and to investigate their insecticidal strength by molecular docking and three-dimensional structure simulation. These studies have cleverly elucidated the mechanisms of action of the EO and NE based on their three-dimensional structure. The interaction between natural product insecticides and ALT and AST activity has been studied, laying the foundation for the development of other anti-insect components and for the investigation of the insecticidal mechanism of other botanical pesticides^[192].

Chitin has important roles in insect growth and development. Chitin is synthesized and decomposed by chitin synthase (CHS) and chitin deacetylase (CDA). The results show that controlling the metabolism of chitin can effectively control diseases and insect pests, which is an important factor to be considered in the process of insecticide research^[193]. The experimental results showed that methylcinderone and methyllicidone can be inhibitors of CHS activity and showed hormone antagonistic activity against juvenile *A. aegypti*. Linderone and methylcinderone are isolated from *Lindera erythrocarpa* (Lauraceae) and have inhibitory activity against CHS activity. Therefore, according to the structure of linderone and methylcinderone, Song et al.^[194] designed and synthesized a series of N-amino-maleimide derivatives containing hydrazone groups. The results showed that the synthesized compounds exhibited effective inhibitory effects on *C. pipiens pallens*. Thus, it can be seen that CHS can cause insect mortality.

5.1.4 Na⁺/K⁺-ATPase and carboxylesterase

Dependence on the ATPase sodium potassium pump maintains the dynamic balance of Na⁺ and K⁺ in cells. The Na⁺/K⁺-ATP enzyme is important for maintaining electrochemical gradients, potential differences, cellular signal transmission and secondary transport in biological cells^[24]. For example, red seaweeds have toxic, growth inhibiting and neurotoxic effects on the dengue vector *A. aegypti*. Some

studies have shown that red seaweeds inhibit *A. aegypti* reproduction by growth inhibition and neurotoxin action^[16].

The main mechanism of carboxylesterase (CARE) is that the compounds containing carboxylic esters are hydrolyzed into alcohols and acids. Recent studies have shown that CARE in insects is one of the most important metabolic detoxification enzymes^[5]. Carboxylesterase, a kind of serinase, is resistant to pesticides containing CARE by degradation in insects. Resistant to pesticides containing phosphate ester and thioester by blocking action. CARE is related to pesticide resistance in insects and can function in the detoxification of many types of insecticides such as organophosphorus pyrethroid and carbamates^[27]. Brown planthopper is the most harmful pests of rice in many parts of Asia. The researchers studied the anti-insect activity of mangosteen fruit extract against brown planthopper and found that mangosteen pericarp extract can inhibit detoxification enzyme. Therefore, this agent can be used as an insecticide substitute to control brown planthopper^[195].

5.2 Effects of other factors

Many botanical insecticides can interfere with the growth and development of insects^[3], for example, affecting the growth and digestive system, nervous system, respiratory system and hormone metabolism effects.

Pesticides from plant sources can have lethal effects by interfering with the nervous system of insects. The main mechanism in operation is that pesticides that pass through the cuticle of the insect or enter the digestive system via ingestion spread to the nerves via the blood lymph circulation, act on the sodium channels of the insect neurons and directly interfere with the transmission of neural signals, causing the excitement of reflective insects, first inhibiting the sympathetic nerve endings, thereby reducing the function of central nervous system and causing death. Eurycomanone, a flavonoid extracted from the long-leaf *Eurycoma longifolia* has an excitatory effect on the central taste neurons of *P. xylostella* and can significantly inhibit the current of the GABAA receptor. It has strong antifeedant activity and can effectively inhibit the growth of *P. xylostella*^[167]. Eurycomanone extracted from *E. longifolia* is a natural insect-resistant component and has obvious antifeedant activity against *P. xylostella*. It can inhibit the growth and development of *P. xylostella* and affect the development of taste receptors of *P. xylostella* larvae. Additionally, it can stimulate the central taste nerve of *P. xylostella* and inhibit the current of the GABAA receptor^[166]. Respiratory metabolism is the basic biochemical process that enables insects to use nutrients, produce energy, maintain life

activities and reproduce. In the past, rotenone was the main plant insecticide acting on the respiratory system of insects^[196]. Its action site is between NADH and coenzyme Q, which blocks electron conduction and affects the synthesis of ATP. Tetrahydrofuran fatty acid lactone is a strong respiratory poison. The main insecticidal components isolated from *Annona squamosa* and *Asimina triloba* have the structure of tetrahydrofuran fatty acid lactone. Rotenone acts on the NADH2 coenzyme Q oxidoreductase coupling site and inhibits oxidative phosphorylation^[197].

Botanical pesticides can inhibit the growth and development of insects by blocking the concentration of ecdysone and juvenile hormones, such as the prothymocytic and hypopharyngeal hormones. Analogues of insect juvenile hormones are insecticides developed in the 1970s. Botanical insecticides can affect the development and reproduction of crustaceans by interfering with the hormone activities of insect juveniles^[198].

6 CONCLUSIONS AND PROSPECTS

The continuous growth of the global population puts forward higher requirements for agricultural production^[199]. According to statistics, there is 17.3 Mha of land used for farming in the world. The top five countries with the total arable land area are the USA (1.67 Mha), India (1.53 Mha), China (1.50 Mha), Russia (1.24 Mha) and Brazil (0.661 Mha). However, crop production is always accompanied by the threat of pests, leading to crop loss^[200]. Synthetic pesticides have the advantages of high speed, high efficiency, broad-spectrum targeting and are suitable for large-scale industrial production. As a result, they are widely used to control crop pests^[201]. In recent years, the overuse and misuse of synthetic pesticides have caused harm to humans and the environment, and caused toxicity to non-target organisms, thus harming biodiversity^[202,203]. The production of biological pesticides generally does not compete for raw materials with synthetic products, and the environmental pollution in the production process is relatively small, which is the development direction advocated and encouraged by the state. All of these are the source of the competitiveness of biological pesticides in the international pesticide market, especially the fundamental reasons for botanical pesticides to maintain market share^[204]. However, in the absence of better alternatives, synthetic pesticides are still the mainstay option for crop protection and are widely used worldwide. Therefore, there is an urgent need to find a better substitute. Through visual analysis technology and literature review, we found that natural products have the advantages of no pollution, easy biodegradation, various modes

of action, low toxicity to non-target organisms and can effectively control crop pests. It has high research value and is expected to become the primary type of insecticide in place of chemical insecticide in the future.

Six kinds of natural products with pesticidal activity have been reviewed in this paper. They exert their pesticidal effect mainly through gastrointestinal toxicity, contact toxicity, systemic action and fumigation. The main mechanism of these natural products is to affect the growth and development of pests by affecting their digestive system, respiratory system, nervous system and metabolic enzymes. This study highlighted that natural products can kill a variety of crop pests, but they have not been widely used as commercial pesticides. We consider that the causes of this lack of progress fall into four areas: sourcing, processing, degradability and review. (1) The source problem is because most of the natural pesticides originate from natural products in plants, and their commercial application requires large-scale planting, which will compete with the cultivation of food. (2) There are many problems in the processing of natural pesticides. These natural products may include plant extracts or *in vitro* phytochemicals containing mixtures of different concentrations of active compounds. There are high-cost raw materials and extraction, purification and formulation steps as well as the difficulty of optimizing the quantity and quality of active ingredients. Due to the need for natural products to extract, separate and purify plants, coupled with the instability of natural products, the processing of natural pesticides brings new problems. For various reasons, the processing of natural products is more complex than synthetic pesticides. Manufacturers are likely to be more interesting in producing synthetic pesticides that achieve more economical scalability and profitability^[205]. (3) The degradability problem is because the natural pesticides easily degrade, which can lead to low utilization. (4) The review problem is because natural pesticides cannot be reviewed in accordance with the review standards of synthetic pesticides, which limits their application in the market. In the face of these difficulties, most pesticide manufacturers are reluctant to invest in the production of natural pesticides, thus limiting their application.

Although some problems in the large-scale application of natural pesticides exist, with the gradual enhancement in awareness of environmental protection, natural pesticides as a novel, environmentally-friendly pesticide will make an important contribution to crop pest control in the future. To realize the desired benefit of natural insecticides in pest control, the problems existing in natural pesticides can be solved in the following ways. (1) Plants that produce natural

pesticides can be planted on land that is not suitable for farming to avoid competition with food crops. (2) To ensure natural pesticides will be widely used in the future, we must develop abundant reserve of natural products because of the supply of materials needed for natural products will be subject to seasonal variations affecting the continuity of their supply^[206]. (3) Natural polymeric materials such as chitosan, starch and sodium alginate are biodegradable, biocompatible and renewable. They are widely used in the hydrogel system^[207]. The use of hydrogels based on natural polymeric materials has evident advantages in that several pesticides are gradually released from the preparation systems. This discovery could solve the challenge of spontaneous degradation of natural insecticides^[122]. (4) It is necessary to formulate a set of testing standards suitable for natural pesticides according to the characteristics of natural products to enable their production to be standardized. The application of natural product pesticides is relatively affected by the environment, and there are many uncertain factors. Therefore, there are many problems to be solved in the quality standardization of

natural product pesticides. Through the understanding of natural product pesticides, we recommend the use of tissue cultures in bioreactors, polyploidization and rapid plant reproduction, ingeniously combined with current science and technology to vigorously support production and processing of natural product pesticides^[208].

Natural and synthetic pesticides have their own advantages and disadvantages, and their combined use is likely to be a major trend in the future. At present, green and pollution-free natural pesticides must be developed as a priority to ensure the rational use of synthetic pesticides. It is necessary to study the mode of action of natural products on pests, increase the development of new dosage forms of natural product pesticides, and improve the diversity and innovation of natural product pesticides in order to ensure a bright future and effective use of natural pesticides. In addition, crop protection is a global problem, so it is necessary to strengthen cooperation between countries and researchers to develop more advanced technologies to produce natural pesticides.

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Compliance with ethics guidelines

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