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Entomopathogenic Microbial Metabolites: Molecular Trends and its Mechanism of Actions Against Insect Pest

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INTRODUCTION

Insect pest in agriculture accounts for severe yield losses of crops globally and their management by conventional practices have become very much challenging among the farming communities. Traditional use of chemical insecticides has played a significant role in managing insect pests but their non-judicious use has causes severe threats to the non-targeted organisms, humans and ecosystem. The indiscriminate and prolong use of chemical pesticides also have resulted in widespread insecticide resistance development among the insect pest of economically important crops. To overcome the problems of insecticide resistance, microbial entomopathogens have emerged as a successful biological alternative to chemicals. These includes entomopathogenic fungi such as *Metarhizium* spp., *Beauveria bassiana*, *Cordyceps* spp., *Lecanicillium lecanii* and bacteria including *Bacillus thuringiensis* (Bt) etc. These entomopathogenic microorganisms can directly penetrate inside the insect body, colonize them and then destroys their body parts by rupturing and making them paralyse and death. Beside these some of the entomopathogens like Bt inside the insect host can produce toxins (Cry toxins) which can rupture the cellular organelles and causes insect septicaemia (Dutta *et al.*, 2023). During host infection, these entomopathogens can also synthesize low molecular weight secondary metabolites that facilitates insect invasion, suppresses immune defences and accelerates insect host mortality. Unlike synthetic insecticides, microbial metabolites exhibit sophisticated molecular mode of action and can target multiple physiological pathways inside the insect body. The multitarget property of secondary metabolites of entomopathogens substantially reduces the problems associate with insecticide resistance and offers an eco-friendly alternative to chemicals in managing insect pest in agriculture.

Recent developments in metabolomics studies with other multi-omics studies such as transcriptomics, proteomics, metagenomics etc. have revolutionize the discovery of novel secondary metabolites of entomopathogens which have insecticidal properties. Beside this, advances in genomic mining and genomic annotation techniques have further revealed the presence of numerous cryptic biosynthetic gene clusters (BGCs) responsible for production of novel unidentified secondary metabolites present in the entomopathogens. Recent developments in CRISPR-Cas based technologies also have provided new insights into metabolic engineering technologies that have open a new avenue for enhancing metabolite production and designing metabolite based insecticidal biopesticides (Sinha *et al*., 2019).

Major Secondary Metabolites of Entomopathogens and its Mechanism of Action

The secondary metabolites produce by the entomopathogenic microorganisms plays essential role in suppressing the insect pest population by reducing its virulence and host colonization capacities. These secondary metabolites include cyclic peptides, polyketides, terpenoids, alkaloids and non-ribosomal peptides and proteins. Entomopathogenic fungi like *B. bassiana* which is popularly known as white muscardine fungus can produce secondary metabolites like beauvericin, bassianolide, bassiacridin etc. which shows cytotoxic and disrupts cellular components in insect host. The green muscardine fungus i.e. *Metarhizium* spp. can produce secondary metabolites like destruxins (A-E), cytochalasins, swainsonine etc. which can disrupt calcium channel and causes paralysis in insect pests. In *Cordyceps militaris*, they can produce secondary metabolites like cordycepin, cordymin etc. which can inhibit the RNA synthesis in insects. Secondary metabolites like lecanicillins produces by entomopathogens like *Lecanicillium lecanii* can cause cuticle degradation in insects thereby increases its mortality rate. Leucinostatins and paecilomide produce by *Purpureocillium lilacinum* can cause mitochondrial disruption and also shows wider insecticidal activity (Gibson *et al*., 2014). Entomopathogenic bacteria like *Bacillus thuringiensis* can produce cry toxins, Vip proteins and β-exotoxins that causes insect septicaemia and paralysis upon infection to the host (Valtierra-de-Luis *et al*., 2020). *Photorhabdus* spp. generally founds associated with the entomopathogenic nematodes and produces remarkable chemical arsenals like stilbenes, photorhabdus toxin complex and other antimicrobial metabolites that helps in disruption of cytoskeleton and causes immune suppression. Similarly, *Xenorhabdus* spp. another bacterium generally associates with *Steinernema* nematodes which can produces wide range of metabolites like xenocoumacins, xenorhabdins which shows both antimicrobial activity and toxicity towards insect pests (Sharma *et al*., 2016). In an over all, entomopathogens initially colonizes the insect host and the biosynthesised secondary metabolites by them releases into the haemocoel or tissue organs of insect pest. These secondary metabolites perform multiple molecular target actions like ionic imbalance, distortion of cytoskeleton and disrupts neuromuscular system which results in paralysis of the insect pests. The pathogenicity attributes of entomopathogens do not solely depends on a single metabolite rather it depends on synergistic interaction among the secondary metabolite's synthesis by the entomopathogens.

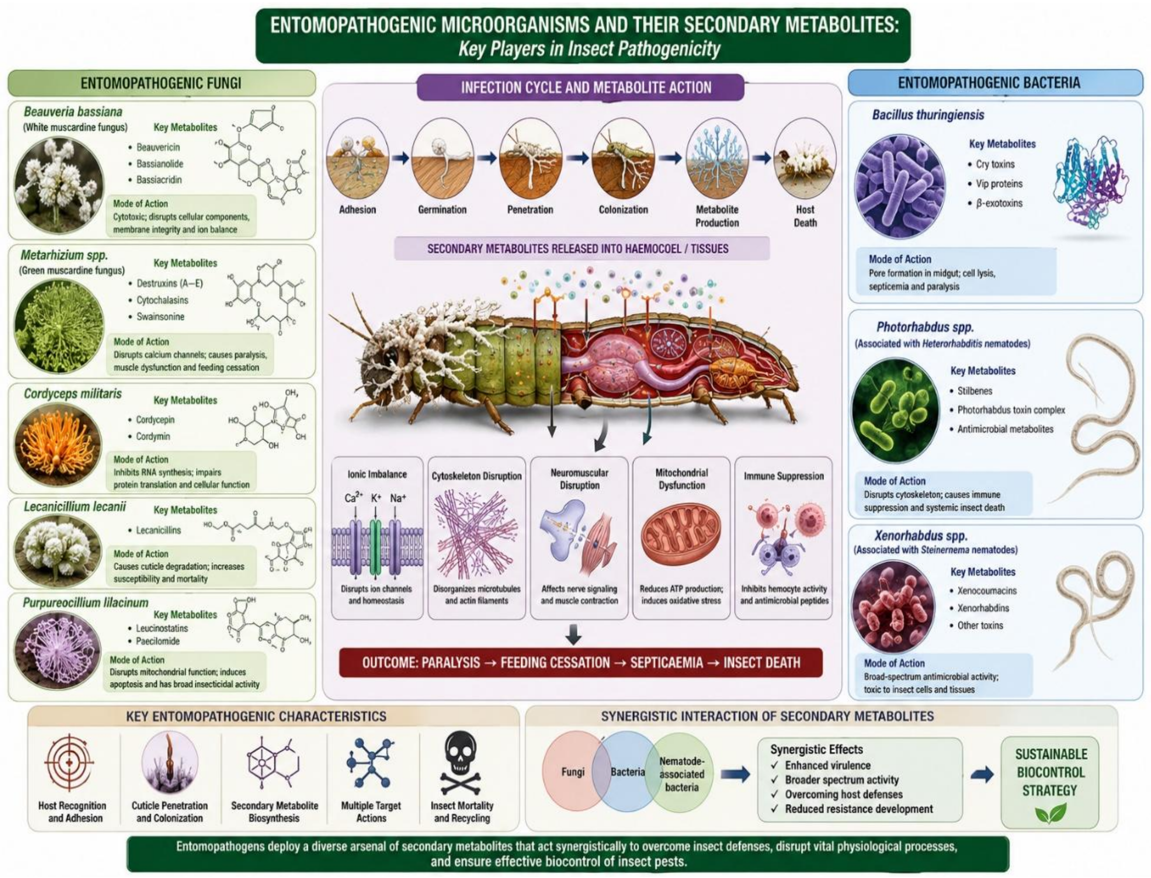

Fig 1: Mechanism of action of secondary metabolites of entomopathogens towards insect pests in agriculture

Molecular Approaches in Secondary Metabolomic Studies of Entomopathogens

The metabolome of entomopathogens is very much dynamic and changes according to the developmental stages, nutrient availability and environmental conditions. The secondary metabolite production by the entomopathogens in the artificial culture medium may differ from the metabolite production during infection. Thus, the metabolite production by entomopathogen varies according to the different species, type of culture medium where they grown and presence of host. The general metabolomics workflow can be represented as:

Genome → Biosynthetic gene cluster → Transcriptional activation → Enzyme production → Metabolite biosynthesis → Metabolite secreation → Host molecular target

The genome of entomopathogens contains the biosynthetic gene clusters (BGCs) for the production of secondary metabolites and enzymes. The metabolites after its biosynthesis it secretes into the insect host and target host at physiological and molecular level (Zhang *et al*., 2020).

The whole genome sequencing of entomopathogens also reveals the metabolomic potential of entomopathogens by providing information about biosynthesis pathways like polyketide synthetase (PKSs), non-ribosomal peptide synthetase (NRPS), hybrid PKSs-NRPS synthetase, terpene synthetases etc (Pedrini, 2022). Beside this, the genome wide association studies also reveal the metabolic diversity within the entomopathogens. Implementation of several bioinformatic platforms like antiSMASH are widely used for identification of silent cryptic genomic regions responsible for secondary metabolite production. Beside this, Liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS) is one of the most powerful approaches for studying entomopathogen secondary metabolites. This LC-MS/MS is particularly used of the identification of non-volatile metabolites and other peptides (de Bekker *et al*., 2013). The integration of proteomics with metabolomics provides additional information at the post transcriptional regulation level. Beside this, integration of metabolomic studies with other multi omics studies and advance technologies like CRISPR-Cas9 and Nanotechnology can provide a comprehensive details and molecular level identification of secondary metabolites present in the entomopathogens.

Table: Major molecular and metabolomic studies in entomopathogenic microbes for identification and determination of secondary metabolites

Molecular approach	Major techniques/platforms	Primary information generated	Application in entomopathogens
Whole-genome sequencing	Illumina, PacBio, Oxford Nanopore	Complete genomic repertoire and biosynthetic potential	Identification of PKS, NRPS, terpene, alkaloid and hybrid biosynthetic genes
Biosynthetic gene cluster (BGC) mining	antiSMASH, PRISM, BAGEL	Prediction of secondary-metabolite biosynthetic clusters	Identification of NRPS, PKS, terpene, siderophore and hybrid clusters
Transcriptomics	RNA-seq, qRT-PCR, single-cell RNA-seq	Differential gene expression	Monitoring activation of secondary-metabolite BGCs during insect infection
Untargeted LC–MS/MS metabolomics	UHPLC-HRMS/MS, QTOF-MS, Orbitrap	Global metabolite fingerprints and molecular features	Detection of known and unknown secondary metabolites during infection
GC–MS metabolomics	GC–MS, GC–HRMS	Volatile and derivatized small metabolites	Analysis of organic acids, fatty acids, amino acids and volatile metabolites
Proteomics	LC–MS/MS proteomics, shotgun proteomics	Protein abundance and enzyme expression	Detection of PKS, NRPS, transporters and metabolic enzymes
Multi-omics integration	Genomics + transcriptomics + proteomics + metabolomics	Integrated molecular phenotype	Linking BGC → gene expression → enzyme → metabolite → host response

CONCLUSION

Entomopathogenic microorganisms represents a promising biocontrol agent for management of insect pest in agriculture. The secondary metabolite produces by the entomopathogens have wider insecticidal properties and can be used for preparation of metabolite based insecticidal formulation. Integration of metabolomic studies with artificial intelligence and other multi omics approaches may help in discovery of novel secondary metabolites present in entomopathogens. Thus, future studies should focus on the integration of metabolomics with genomics, proteomics, transcriptomics and other advances technologies for the discovery of metabolites from entomopathogens and development of bioformulation for management of insect pest in sustainable agricultural practices.

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