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REVIEW ARTICLE

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Endosymbiotic microbes from entomopathogenic nematode (EPNs) and their applications as biocontrol agents for agro-environmental sustainability

Preety Tomar[1], Neelam Thakur[1*] and Ajar Nath Yadav[2]

Abstract

Background: The biological diversity on planet earth is declining day by day, due to different factors such as excessive applications of pesticides. The utilization of chemical pesticides affected environment as well as microorganisms. The awareness among the peoples towards the hazards by the residual toxicity of chemical pesticides should be developed for agro-environmental sustainability.

Main body: Entomopathogenic nematodes (EPNs) are the bacto-helminth parasites which show classical mutualism with the genera *Xenorhabdus* and *Photorhabdus*. The nematodes along with its endosymbiotic bacteria have a biocontrol potential which could be used to reduce chemical pesticides. Applications of bioagents have been reported and resulted in considerable reduction in pathogens. Furthermore, these bioagents are biodegradable, eco-friendly and easy to apply for protection of crops against diverse pathogenic organism. The nematode-bacterium complexes are effective against huge range of bacteria, fungi, nematodes and insects that are harmful to the crops. Along with biocontrol potential, the endosymbionts produce diverse secondary metabolic compounds, exoenzymes and toxic compounds that show antibiotic, antimycotic, nematicidal, miticidal and anticancerous properties.

Conclusion: The present review deals with the diversity of endosymbiotic microbes from EPNs and their role in biocontrol for the agro-environmental sustainability.

Keywords: Agricultural sustainability, Biocontrol, Diversity, Entomopathogenic nematode, *Photorhabdus*, *Xenorhabdus*

Background

Entomopathogenic nematodes (EPNs) are microscopic roundworms that belong to the families Heterorhabditidae and Steinernematidae of phylum Nematoda. EPNs are beneficial nematodes that exhibit a holoparasitic mode of survival (Bhat et al. 2020). The EPNs have been reported to survive in most of environmental conditions except psychrophilic conditions of Antarctica (Hominick 2002). The EPNs from genus *Steinernema* and *Heterorhabditis* were considered deadly fatal for a number of agricultural insects (Liu et al. 2020). Globally, 17 species of genus *Heterorhabditis* and 100 species of genus *Steinernema* have been reported that are found to be lethal for insect pests (Bhat et al. 2020). These nematodes showed mutualistic associations with endosymbiotic bacterial species that live inside the nematode. A major role has been played by these bacterial endosymbionts in nutritional physiology (Feldhaar 2011). The endosymbionts *Xenorhabdus* and *Photorhabdus* reside in symbiotic

*Correspondence: neelamthakur@eternaluniversity.edu.in

[1] Department of Zoology, Akal College of Basic Sciences, Eternal University, Sirmour 173101, India
Full list of author information is available at the end of the article

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association with EPNs *Steinernema* and *Heterorhabditis* (Kaya and Gaugler 1993).

In EPNs, the third-stage juvenile (dauer juvenile) resides freely in soil with non-foraging behaviour, and carries endosymbiotic bacteria inside the body which is responsible for causing the pathogenicity in their host. Once the dauer juvenile penetrates into the host body through spiracles or through natural body openings, it releases its symbiotic bacteria inside the haemocoel of the insect. The bacterial cells duplicate and generate severe toxins that have a high insecticidal potential and can assassinate its host in less than 2 days (Adams and Nguyen 2002). The infected host dies soon after infection due to contagion. Within the insect cadaver, these bacteria nourish the EPNs and promote the growth and reproduction of EPNs. As the food availability shortens, the dauer juvenile of EPNs comes out of the cadaver and look for a new host. Applications of EPNs with their bacterial endosymbionts become a prime approach in the biocontrol sector as well as in integrated pest management. Moreover, these EPNs now become model organisms and used widely in the fields such as evolutionary biology, biological control, soil ecology as well as the bacterial symbiotic mutualism (Stock 2015). Emerging dissatisfaction due to the excessive applications of chemicals insecticides for insect pest control has increased, as they showed adverse effects on the environment and human health (Tomar et al. 2022). Thus, it has turned out to be essential to diminish the utilization of these insecticides and replaces those using ecologically safer products in a sustainable agriculture perspective.

In recent times, these beneficial endosymbionts become a treasure trove for insecticidal compounds as well as for different bioactive compounds. The endosymbionts can decrease the chemical insecticides used in insect control and plant protection by stabilizing the environmental changes (Thakur et al. 2020, 2021; Migunova and Sasanelli 2021). Undoubtedly, these endosymbionts may become a favourable substitute in increasing the biological control of numerous phyto-insect pests as well as pathogens. EPN-associated bacterial endosymbionts have a high potentiality for agricultural pest control due to the toxic compounds and proteins produced as secondary metabolites (Thakur et al. 2022a, 2022b). The present review deals with distribution, identification and culturing practices of endosymbionts associated with EPNs. The major emphasis has been laid on the bioactive compounds produced by the endosymbionts.

Main body

Entomopathogenic nematode

Since the seventeenth century or possibly prior to these EPNs were familiar (Nguyen and Smart Jr 2004) although in the nineteenth and twentieth century's vast studies on EPNs were carried out, and it was reported that EPNs were distributed worldwide. Steiner was the first to expound the EPN as *Aplectana kraussei* (*Steinernema kraussei*) from a hymenopterous sawfly (Steiner 1923), followed by *Neoplectana glaseri* from *Popillia japonica* (scarabaeid beetle) (Steiner 1929), *S. feltiae*, *S. affinae,* and *S. carpocapsae* were from *Cydia pomonella* (Weiser 1955). Mracek (2002) reported that the nematodes as most victorious organisms on earth which have been found nearly all types of habitats. In India, various investigations have been accomplished to find out the new EPNs species that resulted in the isolation of a new *H. indica* species from Coimbatore, Tamil Nadu (Poinar Jr et al. 1992). EPNs species were previously described as an excellent means of biocontrol for the management of agricultural insect pests. Till now, 11 EPNs species were disclosed in India including *Heterorhabditis indica, H. bacteriophora, S. sangi, S. bicornutum, S. abbasi* (*S. thermophilum), S. siamkayai, S. carpocapsae* (*S. meghalayense*)*, S. riobrave, S. glaseri, S. surkhetense,* and *S. hermaphroditum* (*S. dharanai*) (Lalramnghaki 2017).

Distribution of endosymbionts of EPNs

The nematodes of families Steinernematidae and Heterorhabditidae have gained the interest of humanity towards their promising biocontrol capacity of managing insect population (Singh et al. 2022). *Xenorhabdus* and *Photorhabdus,* the Gram-negative bacteria, are endosymbionts of the dauer juvenile (IJ_3) phase of EPNs. The IJs can perforate the insect via natural body orifice. It liberated the endosymbionts inside the blood stream of the host upon getting entry inside the host. Inside the host blood stream, the bacterial cells reciprocated. The occurrence of huge bacterial cells in the host midgut resulted in demises of insect after 24–48 h (Kaya and Gaugler 1993). Huge numbers of *Xenorhabdus* and *Photorhabdus* have been reported as endosymbionts from *Steinernema* and *Heterorhabditis* (Tables 1, 2).

Taxonomy of endosymbionts

Bacterial groups are considered as the most diversified biological group having varied phylogeny of the organisms (Adams et al. 2006). The fossil traces of cyanobacteria were found about 2.9 billion years back, and the presence of nematodes was supposed somewhat earlier in the Cambrian radiation (Noffke et al. 2003). In the mid-Paleozoic era, it has been considered that the primogenitor of family Heterorhabditidae and Steinernematidae started to reconnoitre their symbiotic interactions with the members of Enterobacteriaceae (Poinar Jr 1993). *Achromobacter nematophilus* was the first endosymbiont found in mutualistic association with *Neoaplectana*

Table 1 Global distribution of endosymbionts *Xenorhabdus*

Endosymbiotic bacteria	Nematode species	Host organism	Country	References
Xenorhabdus szentirmaii	*Steinernema rarum*	*Galleria mellonella*	Argentina	Lengyel et al. (2005)
Xenorhabdus miraniensis	*Steinernema* spp.	*G. mellonella*	Australia	Tailliez et al. (2006)
Xenorhabdus magdalenensis	*Steinernema australe*	*G. mellonella*	Chile	Tailliez et al. (2012)
Xenorhabdus ehlersii	*Steinernema longicaudum*	*G. mellonella*	China	Lengyel et al. (2005)
Xenorhabdus ishibashii	*Steinernema aciari*	*G. mellonella*	China	Kuwata et al. (2013)
Xenorhabdus budapestensis	*Steinernema ceratophorum*	*G. mellonella*	China	Yang et al. (2012a, b)
X. szentirmaii	*Steinernema costaricense*	*G. mellonella*	Costa Rica	Lengyel et al. (2005)
Xenorhabdus poinarii	*Steinernema cubanum*	*G. mellonella*	Cuba	Fischer-Le Saux et al. (1999)
Xenorhabdus bovienii	*Steinernema poinari*	*G. mellonella*	Czech Republic	Sajnaga et al. (2018)
Xenorhabdus nematophila	*Steinernema carpocapsae*	*Cydia pomonella*	Czechoslovakia	Martens and Goodrich-Blair (2005)
X. bovienii	*Steinernema feltiae*	*Feltia segetum (Agrotis segetum)*	Denmark	Ehlers et al. (1997)
Xenorhabdus indica	*Steinernema yirgalemense*	*G. mellonella*	Ethiopia	Tamiru et al. (2012)
Xenorhabdus kozodoii	*Steinernema boemarei*	*G. mellonella*	France	Tailliez et al. (2006)
X. poinarii	*Steinernema khuongi*	*G. mellonella*	Florida	Baniya and DiGennaro (2021)
Xenorhabdus doucetiae	*Steinernema diaprepesi*	*Diaprepes abbreviates*	Florida	Tailliez et al. (2006)
X. bovienii	*Steinernema silvaticum*	*G. mellonella*	Germany	Akhurst and Boemare (1988)
Xenorhabdus spp.	*Steinernema kraussei*	*Cephaleia abietis*	Germany	Akhurst (1982b)
X. bovienii	*Steinernema tbilisiensis*	*G. mellonella*	Georgia	Gorgadze et al. (2015)
X. griffiniae	*Steinernema hermaphroditum*	*G. mellonella*	Indonesia	Tailliez et al. (2006)
X. kozodoii	*Steinernema vulcanicum*	*G. mellonella*	Italy	Clausi et al. (2011)
X. bovienii	*Steinernema ichnusae*	*G. mellonella*	Italy	Tarasco et al. (2011)
Xenorhabdus japonicus	*Steinernema kushidai*	*G. mellonella*	Japan	Nishimura et al. (1994)
X. bovienii	*Steinernema litorale*	*G. mellonella*	Japan	Özdemir et al. (2020)
Xenorhabdus sp.	*Steinernema monticolum*	*A. segetum; A. ipsilon, arapediasia teterrella*	Korea	Kang et al. (2003)
X. hominickii	*Steinernema karii*	*G. mellonella*	Kenya	Tailliez et al. (2006)
X. stockiae	*Steinernema surkhetense*	*G. mellonella*	Nepal	Bhat et al. (2017)
X. romanii	*Steinernema puertoricense*	*G. mellonella*	Puerto Rico	Tailliez et al. (2006)
X. kozodoii	*Steinernema arenarium*	–	Russia	Tailliez et al. (2006)
X. khoisanae	*Steinernema beitlechemi*	*G. mellonella*	South Africa	Cimen et al. (2016a)
X. khoisanae	*Steinernema fabii*	*G. mellonella*	South Africa	Abate et al. (2018)
X. indica related endosymbiont	*Steinernema biddulphi*	*G. mellonella*	South Africa	Cimen et al. (2016b)
X. bovienii	*Steinernema citrae*	*G. mellonella, Tenebrio molitor*	South Africa	Stokwe et al. (2011)
X. khoisanae	*Steinernema jeffreyense*	*G. mellonella*	South Africa	Dreyer (2018)
X. khoisanae	*Steinernema khoisanae*	*G. mellonella*	South Africa	Ferreira et al. (2013)
Xenorhabdus griffiniae	*Steinernema litchii*	*G. mellonella*	South Africa	Dreyer (2018)
Xenorhabdus khoisanae	*Steinernema sacchari*	*Eldana saccharina, G. mellonella*	South Africa	Dreyer (2018)
Xenorhabdus budapestensis	*Steinernema bicornutum*	*G. mellonella*	Serbia	Lengyel et al. (2005)
X. indica	*Steinernema abbasi*	*G. mellonella*	Sultanate of Oman	Tsai et al. (2008)
Xenorhabdus stockiae	*Steinernema siamkayai*	*G. mellonella*	Thailand	Ardpairin et al. (2020)
X. poinarii	*Steinernema glaseri*	*Popillia japonica*	USA	Akhurst (1983b)
Xenorhabdus cabanillasii	*Steinernema riobrave*	*Helicoverpa* zea	USA	Tailliez et al. (2006)
Xenorhabdus koppenhoeferii	*Steinernema scarabaei*	*Anomala orientalis*	USA	Tailliez et al. (2006)
X. bovienii	*Steinernema intermedium*	*G. mellonella*	USA	Akhurst (1983b)
Xenorhabdus mauleonii	*Steinernema* spp.	*G. mellonella*	USA	Tailliez et al. (2006)
Xenorhabdus innexi	*Steinernema scapterisci*	*Scapteriscus vicinus*	*Scapteriscus vicinus*	Kim et al. (2017)
Xenorhabdus vietnamensis,	*Steinernema sangi*	*G. mellonella*	Vietnam	Kämpfer et al. (2017)
Xenorhabdus thuongxuanensis	*Steinernema sangi*	*G. mellonella*	Vietnam	Kämpfer et al. (2017)
Xenorhabdus eapokensis	*Steinernema eapokense*	*G. mellonella*	Vietnam	Kämpfer et al. (2017)

Table 2 Global distribution of endosymbionts *Photorhabdus*

Endosymbiotic bacteria	Nematode species	Host organism	Country	References
Photorhabdus luminescens subsp. *luminescens*	*Heterorhabditis bacteriophora*	*Heliothis punctigera*	Australia	Machado et al. (2018)
Photorhabdus luminescens subsp. *laumondii*	*H. bacteriophora*	*H. punctigera*	Australia	Tailliez et al. (2010)
Photorhabdus luminescens subsp. *kayaii*	*H. bacteriophora*	*H. punctigera*	Australia	Tailliez et al. (2010)
Photorhabdus luminescens subsp. *thracensis*	*H. bacteriophora*	*H. punctigera*	Australia	Machado et al. (2018)
Photorhabdus khanii	*H. bacteriophora*	*H. punctigera*	Australia	Tailliez et al. (2010)
Photorhabdus caribbeanensis	*H. bacteriophora*	*H. punctigera*	Australia	Machado et al. (2018)
Photorhabdus asymbiotica	*Heterorhabditis gerrardi*	*Tenebrio mollitor*	Australia	Akhurst et al. (2004)
Photorhabdus australis subsp. *australis*	*H. gerrardi*	*T. mollitor*	Australia	Plichta et al. (2009)
Photorhabdus luminescens subsp. thailandensis	*H. gerrardi*	*T. mollitor*	Australia	Machado et al. (2021)
Photorhabdus australis	*H. gerrardi*	*T. mollitor*	Australia	Machado et al. (2018)
Photorhabdus subsp. *guanajuatensis*	*Heterorhabditis atacamensis*	*G. mellonella*	Chile	Machado et al. (2019)
Photorhabdus bodei	*Heterorhabditis beicherriana*	*G. mellonella*	China	Machado et al. (2018)
Photorhabdus luminescens subsp. *luminescens*	*Heterorhabditis floridensis*	*G. mellonella*	Florida	Blackburn et al. (2016)
Photorhabdus luminescens subsp. *akhurstii*	*Heterorhabditis georgiana*	*G. mellonella*	Georgia	Machado et al. (2018)
Photorhabdus stackebrandtii	*H. georgiana*	*G. mellonella*	Georgia	Machado et al. (2018)
Photorhabdus kleinii	*H. georgiana*	*G. mellonella*	Georgia	Machado et al. (2018)
Photorhabdus luminescens subsp. *akhurstii;*	*H. indicus*	*Scirpophaga excerptalis*	India	Machado et al. (2021)
Photorhabdus aegyptia	*Heterorhabditis indicus*	*S. excerptalis*	India	Machado et al. (2021)
Photorhabdus asymbiotica	*H. indicus*	*S. excerptalis*	India	Machado et al. (2021)
Photorhabdus temperata	*Heterorhabditis downesi*	*G. mellonella*	Ireland	Machado et al. (2018)
Photorhabdus cinerea	*H. downesi*	*G. mellonella*	Ireland	Machado et al. (2018)
Photorhabdus luminescens subsp. *mexicana*	*Heterorhabditis maxicana*	*G. mellonella*	Mexico	Machado et al. (2019)
Photorhabdus luminescens subsp. *sonorensis*	*Heterorhabditis sonorensis*	*G. mellonella*	Mexico	Orozco et al. (2013)
Photorhabdus heterorhabditis	*Heterorhabditis zealandica*	*Heteronychus arator*	New Zealand	Ferreira et al. (2014)
Photorhabdus luminescens subsp. *laumondii*	*Heterorhabditis safricana*	*G. mellonella*	South Africa	Geldenhuys et al. (2016)
Photorhabdus luminescens subsp. *noenieputensis*	*Heterorhabditis noenieputensis*	*G. mellonella*	South Africa	Ferreira et al. (2013)
Photorhabdus hainanensis	Undescribed spp.	*G. mellonella*	South Africa	Tailliez et al. (2010)
Photorhabdus namnaonensis	*H. baujardi*	*G. mellonella*	Thailand	Glaeser et al. (2017)
Photorhabdus temperate	*Heterorhabditis megidis*	*Popillia japonica*	USA	Toth and Lakatos (2008)
Photorhabdus cinerea	*Heterorhabditis megidis*	*P. japonica*	USA	Machado et al. (2018)
Photorhabdus tasmanensis	*Heterorhabditis marelatus*	*G. mellonella*	USA	Machado et al. (2018)
Photorhabdus luminescens	*Heterorhabditis baujardi*	*G. mellonella*	Vietnam	Glaeser et al. (2017)

carpocapsae Weiser (Poinar Jr and Thomas 1965). The characteristic features of *A. nematophila* did not suit with any of the previously approved genera that results in the emergence of the novel genera *Xenorhabdus*. This novel genus includes bacterial symbionts *X. luminescens* and *X. nematophilus* (Akhurst 1983a). A noticeable separation of *X. luminescens* among the other *Xenorhabdus* genera was based upon the phenotype as well as the genotype of the individual (Boemare and Akhurst 1988) that suggest the establishment of new genera *Photorhabdus* having mutualistic association with the nematodes of genera *Heterorhabditis* (Boemare et al. 1993). The earlier classification of *Xenorhabdus* and *Photorhabdus* into separate genera is completely based upon their phenotypic characters as well as on the mechanism of symbiosis exhibited by them (Thomas and Poinar Jr 1979). After that, the taxonomy of prokaryotes was done through a multiphase prospective that include the combined information of various types of genotype and phenotypes. This multiphase perspective is further followed by molecular biology techniques including DNA-DNA hybridization and sequence analysis of 16S rRNA gene that turns out to be the foundation of the bacterial classification (Stackebrandt 2006).

New species of endosymbionts were discovered by following the 98.7% relatedness concept of 16S rRNA gene, still an initial move towards identification along with the threshold of 70% in DNA-DNA hybridization and the threshold of 80% in DNA-DNA hybridization for efficiently balancing negligible criterion in the bacterial taxonomy approach (Goris et al. 2007). The gene

sequencing technique 16 R-gene for classification was regarded as inappropriate because of little differences along with lateral gene transfer (LTG) (Tailliez et al. 2010). The multilocus sequence analysis (MLSA) technique has been extensively utilized for the recognition of many noval species of bacteria (Liu et al. 2017). The enhanced sequencing methodologies permit the utilization of whole genetic sequence for the identification and classification (Lee et al. 2016). A remarkable potential of genome taxonomy has been shown in the high-resolution classification of genera *Photorhabdus* (Machado et al. 2018).

Life history of endosymbionts

The EPNs are the organisms that cause diseases in insects. In the nematode life cycle specialized infective juvenile (IJ_3) is the only form that lives outside the host insect (Poinar Jr et al. 1979). Inside the intestinal tract of infective juvenile these symbiotic bacteria populate. The other juvenile stages IJ_1 and IJ_2 cannot live without their host and do not carry symbiotic bacteria in their intestinal tract. The endosymbionts (*Photorhabdus* and *Xenorhabdus*) of EPNs exhibit almost similar life cycles. The infective juvenile works as a carrier in transmitting the bacterial endosymbionts (Sicard et al. 2004). Upon entering to the insect body, nematode moves to the haemocoel cavity of the insect and released its endosymbionts. These endosymbiotic bacteria have the ability to escape from the insect immune system and are responsible for causing pathogenicity in the insects by releasing a variety of insecticidal toxins (Koppenhöfer et al. 2007).

In addition to pathogenicity against insects, these bacteria defend the insect cadaver from invading microorganisms (pathogens, competitors, and predators) by producing antimicrobial compounds and also contribute to nematode reproduction (Gulcu et al. 2012). Inside host insect nematodes undergo about 2–3 rounds of reproduction before the nutrients depleted after that infective juvenile (IJ_3) form way out from the insect corpse and seek for a new host (Grewal and Georgis 1999).

Photorhabus bacteria are the endosymbionts of *Heterorhabditis* that make a colony behind the basal bulb in the anterior portion of the intestine. They were also reported scattered in the remaining portion of the intestine (Ciche et al. 2003). The *Xenorhabdus* are endosymbionts of *Steinernema* that colonize in the specific bilobed vesicle of intestine (Martens et al. 2003). The life cycle exhibited by these bacteria is quite unique and interesting as they lived in symbiotic association with nematode and are pathogenic to harmful insects. The endosymbiotic complexes of *Steinernema* show a very high resemblance with *Heterorhabditis* and have a little variability in their life cycle that leads to the independent classification of the two genera. Endosymbiont *Photorhabdus* are emanated via the anterior region, *i.e.* mouth of nematode (Ciche et al. 2008), whereas *Xenorhabdus* is liberated from the posterior region, via anus, of the nematode (Sicard et al. 2004). Host immune suppressing proteins were released by *Steinernema* that might support their endosymbionts release (Simoes and Rosa 1998) but in *Heterorhabditis*, this process is still mysterious (Forst and Clarke 2002). Brillard et al. (2002) reported that both genera show haemotoxic behaviour.

The endosymbionts of both genera release certain protein toxins as well as exoenzymes that are responsible for causing septicaemia in host insects that leads to insect death (Forst and Clarke 2002). In the late infectious state, the proteinaceous toxins produced by bacteria damaged the midgut of the insect mainly the epithelium lining (Silva et al. 2002) (Figs. 1, 2). *Xenorhabdus* and *Photorhabdus* exhibit colony pleomorphism, i.e. phase variation phenomenon in which coexistence of two different variants was observed in single bacterial species. Differences in trait numbers were observed in these variants like release of antibiotics, proteins, pigment substances, lipases, and bioluminescence (Turlin et al. 2006). The endosymbiotic bacteria show two phases in their life cycle that are morphologically distinct from each other. In *Xenorhabdus* spp., the cells under phase I are somewhat larger, mobile with crystalline inclusion bodies and liberate secondary metabolic substances such as lipases, proteases, and some other bioactive components. Phase II cells are much smaller than phase I, immobile and can easily be recognized by staining with dyes (triphenyltetrazolium chloride and bromothymol blue). The cells in phase I condition when exposed to nutritional media having the fusion of two dyes triphenyltetrazolium chloride and bromothymol blue, they shows clearly distinct dark blue bacterial colonies with red core. But an exemption was also noticed that phase I bacterial cells do not absorb dye (bromothymol blue). It has stated that in two phases of their life cycle, the phase I bacteria was normally found in association with reproducing nematodes, while the phase II bacteria were found in the nematode infected cadaver (Turlin et al. 2006).

Culturing practices and cost effectiveness of endosymbionts

The endosymbionts *Xenorhabdus* and *Photorhabdus* can be easily isolated from the dead larval cadaver of *Galleria mellonella* L. infected with IJs of EPNs after 24 h. The infected cadavers should be sanitized with merthiolate (0–1% for 120–180 min) and cleaned multiple times with distilled water. After that transferred to the yeast-soy-based (YS) broth and changed into suspension with the help of tissue homogenizer.

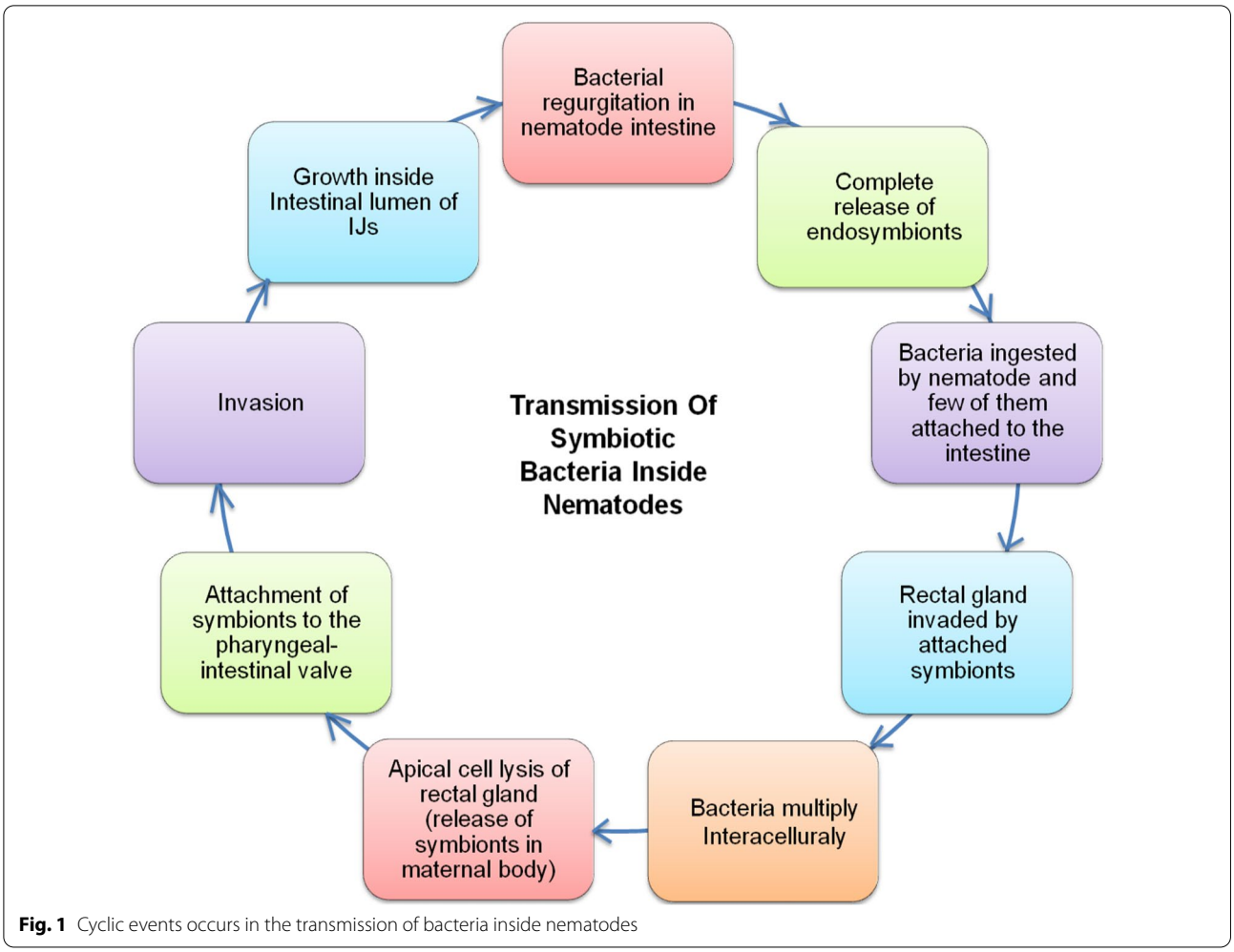

Fig. 1 Cyclic events occurs in the transmission of bacteria inside nematodes

The suspension should be spread over the nutrient agar (NA) containing bromothymol blue and triphenyltetrazolium chloride. The endosymbionts can be isolated using hanging drop system method. The dead cadavers should be soaked into absolute ethanol for surface cleaning and allowed to dehydrate in sterile Petri dish. With the help of a sterilized forceps, dead cadaver should be dissected and a drop of haemolymph dragged out using a sanitized loop. The loop containing haemolymph streaked over the NBT agar and should be placed at room temperature for growth (Poinar and Thomas 1966). An alternative approach for endosymbionts isolation was by directly crushing the IJs. The IJs (50-100IJ) have sterilized with thiomersal (1% for 2 h) and centrifuged. After centrifugation the pellet containing IJs should be washed several times and placed onto nutrient broth (NB) luria–bertani (LB), tryptic soy broth (TSB). The suspension should be spread over the NBT agar media or luria–bertani media and cultivated at room temperature.

Role of endosymbionts as biocontrol agents

Endosymbionts metabolism produces a wide range of secondary metabolites for potential applications in different sectors. In EPNs infected insects, these endosymbionts defend the host cadaver from the invading microbiome by the secretion of a variety of compounds possessing antibiotic activities. These metabolites are also used as biocontrol negotiators for the management of viruses, fungi, nematodes, and insects (Lulamba et al. 2021). The bioactive components produced by *Xenorhabdus* and *Photorhabdus* play an essential role in the biological transformation of host insects. Production of different kinds of antibiotics, proteases, adhesions, lipases, and haemolysins were observed from endosymbionts. Even a single *Xenorhabdus* strain produces multiple metabolites that act against variety of pathogenic organisms. Webster et al. (2002) recorded the productions of several antimicrobials such as β-lactam carbapenem, isopropylstilbenes from *Photorhabdus* species. The discovery of such antimicrobial complexes acquires

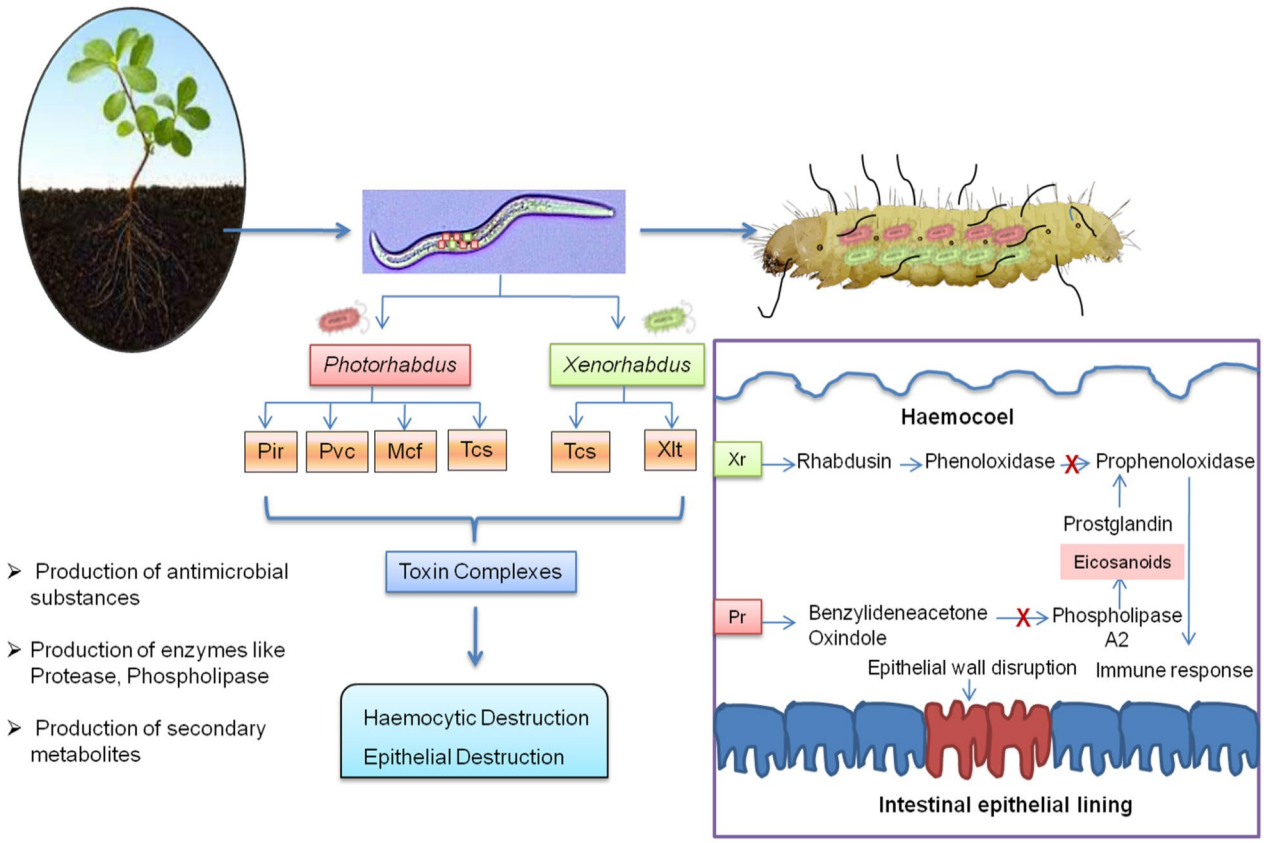

Fig. 2 Action mechanisms of toxic compounds produced by endosymbionts

major attention of agronomic and pharma industries (Hazir et al. 2016) (Tables 3, 4). Numerous bactericidal, fungicidal, entomopathogenic as well as nematode killing activities have been reported from endosymbionts (Muangpat et al. 2020). All the metabolic complexes that showed different activities against insects, parasites, fungi, and viruses were possessed a particular gene that encoded for particular traits (da Silva et al. 2020). Various strains of *Xenorhabdus* produces a variety of secondary metabolites that show a wide range of bioactivity, antibacterial activities, antifungal activities, nematicidal activities, insecticidal activities as well as several cytotoxic properties (Brachmann and Bode 2013) (Tables 3, 4).

Insecticidal activity

Insecticidal activities are the insect killing or insect controlling mechanisms, showed by *Photorhabdus* and *Xenorhabdus.* Nematodes penetrate the host body through naturalistic orifices and liberate the bacteria through defecation that releases compounds that suppress the insect immunity (Webster et al. 2002). They have been found to infect *Cydia pomonella, Delia radicum Diaprepes abbreviates, Thrips* spp., *Otiorhynchus sulcatus, Phyllopertha horticola* as well as the larvae of several other insect orders including dipterans and lepidopterans (Georgis et al. 2006). Several *X. nematophila* strains produce UnA protein that inhibits the accumulation of haemocytes which results in the formation of cover or sheath around the bacteria and nematode (Ribeiro et al. 2003). Dunphy and Webster (1991) reported that these protein and lipopolysaccharides in *G. mellonella* stop the cluster formation of haemocytes that hinder phenoloxidase activation which is a major tool of insect immune system (Forst et al. 1997). Eicosanoids responsible for the cellular immunity in insect's also suppressed by *X. nematophila* strains. They hinder the action of phospholipase A_2 (PLA_2) upon which the production of eicosanoids depends (Kim et al. 2018). Without eicosanoids, insects were died due to acute bloodstream infection or septicaemia. An insecticidal protein (57 kDa) produced by *X. budapestensis* D43 trigger the phenoloxidase cascade in *G. mellonella* and resulted in extreme immune responses such as productions of a high amount of quinones (Yang et al. 2012a, b). This extreme production of quinine is lethal for the insect larvae. Even

Table 3 Bioactive complexes produced by *Xenorhabdus*

Bacterial Spp	Bioactive complexes/secondary metabolite	Biological asset	References
X. beddingii	R-type bacteriocins	Bactericidal	Boemare et al. (1992)
X. bovienii	Xenocyloins	Insecticidal	Proschak et al. (2014)
	Amicoumacin	Antibacterial, insecticidal, antifungal, anti-cancer, and anti-inflammatory	Park et al. (2016)
	Indoles	Antibiotic	Li et al. (1995a)
	Dithiolopyrrolones	Antibiotic	Li et al. (1995a)
X. budapestensis	Bicornitun	Antibacterial and antifungal	Tobias et al. (2017)
	GP-19	Antibacterial and antifungal	Xiao et al. (2012)
	EP-20	Antifungal	
	Fabclavine	Antibacterial, antifungal, antiprotozoal and cytotoxic	Wenski et al. (2020)
X. cabanillasii	Nemaucin	Antibacterial and antifungal	Gualtieri et al. (2012)
	Rhabdopeptide	Antiprotozoal, insecticidal and cytotoxic	Reimer et al. (2013)
	Cabanillasin	Antifungal	Houard et al. (2013)
X. doucetiae	Xenoamicin	Antiprotozoal	Bode et al. (2017)
	Xenorhabdin	Antibacterial	
	Xenocoumacin	Antibacterial, antifungal and antiulcer	
X. indica	Taxlllaids	Antiprotozoal and cytotoxic	Kronenwerth et al. (2014)
X. kozodoii	Xenocoumacin	Antibacterial, antifungal and antiulcer	Tobias et al. (2017)
Xenorhabdus Spp	Xenobactin	Antibacterial and antiprotozoal	Grundmann et al. (2013)
X. khoisanae strain SB10	PAX lipopeptides	Antimicrobial	Booysen et al. (2021)
	Xenocoumacin	Antimicrobial	Booysen et al. (2021)
X. innexi	Rhabdopeptides	Antiprotozoal, insecticidal and cytotoxic	Hacker et al. (2018)
X. mauleonii	Xenoamicin	Antiprotozoal	Tobias et al. (2017)
	and xenocoumacin	Antibacterial, antifungal and antiulcer	
	xenorhabdin	Antibacterial	
X. nematophila	Pristinamycin	Antibacterial	Brachmann et al. (2012)
	Xenorhabdins	Antibacterial	Qin et al. (2013)
	Xenorxides	Antibacterial and antifungal	
	PAX peptides	Antibacterial and antifungal	Hazir et al. (2016)
	Nematophin	Antibacterial and antifungal	Cai et al. (2017)
	Xenocin	Antibacterial	Rathore (2013)
	Xenorhabdicin (R-type bacteriocins)	Antibacterial	Eugenia Nuñez-Valdez et al. (2019)
	Xenocoumacins	Antibacterial, antifungal and antiulcer	Guo et al. (2017)
	Xenortides	Antiprotozoal and cytotoxic	Esmati et al. (2018)
	Rhabdopeptides	Antiprotozoal, insecticidal and cytotoxic	Zhao et al. (2018)
	Xenematides	Antibacterial and insecticidal	Crawford et al. (2012)
	Rhabducin	Insecticidal	Crawford et al. (2012)
	Benzylidene-acetone	Antibacterial, immuno-suppressant and insecticidal	Ji et al. (2004)
X. szentirmaii	Fabclavines	Antibacterial, antifungal, antiprotozoal and cytotoxic	Wenski et al. (2020)
	Szentiamide	Antibacterial, antifungal and cytotoxicity	Nollmann et al. (2015)
	Xenofuranones A and B	Insecticidal	Dongare et al. (2021)
	Xenocoumacin	Antimicrobial	Dreyer et al. (2019)
	PAX lipopeptides	Antimicrobial	Dreyer et al. (2019)

Table 4 Bioactive complexes produced by *Photorhabdus*

Bacterial Spp	Bioactive complexes/secondary metabolite	Biological asset	References
Photorhabdus luminescens	Anthraquinone	Insecticidal	Zhou et al. (2019)
	3,5-Dihydroxy-4-isopropylstilbene 1,3-Dihydroxy-2-(isopropyl)-5-(2-phenylethenyl)benzene	Antifungal, antibiotic	Eleftherianos and Revenis (2011)
	1,6-Dihydroxy-4-methoxy-9,10-anthraquinone	Antibiotic	Richardson et al. (1988)
	1,8-Dihydroxy-3-methoxy-9,10-anthraquinone 1-Hydroxy-2,6,8-trimethoxy-9,10-anthraquinone 1,4-Dihydroxy-2,5-dimethoxy-9,10-anthraquinone	Antibiotic	Hu et al. (1998)
	Carbapenem	Antibiotic	Derzelle et al. (2002)
	GameXpeptides	Cytoxic	Nollmann et al. (2015)
	Indigoidine	Antibiotic	Brachmann et al. (2012)
	Indole	Nematicidal	Hu et al. (1999)
	Lumizinone A	Cytotoxic	Park and Crawford (2016)
	Phurealipids	–	Nollmann et al. (2015)
	Photobactin	Antibiotic	Ciche et al. (2003)
	Pyrone	Antimycotic, Cytotoxic	Hickey et al. (2021)
	Stilbene and its derivatives	Nematicidal, Antibacterial, Antimycotic, Insecticidal	Tobias et al. (2017)
	Trans-cinnamic acid	Antimycotic	Bock et al. (2014)
	Rhabduscin	Insecticidal	Eugenia Nuñez-Valdez et al. (2019)
Photorhabdus temperata	Anthraquinone (1,3-dimethoxy-8-hydroxy-9,10-anthraquinone and 3-methoxychrysazine)	Insecticidal	Yang et al. (2019)
	Benzaldehyde	Antimycotic	Ullah et al. (2014)
	Stillbene	Insecticidal	Shi et al. (2017)
Photorhabdus asymbiotica	Glidobactin/Cepafungin I	Insecticidal	Theodore et al. (2012)
Photorhabdus spp.	Galtox	Insecticidal	Ahuja et al. (2021)

programmed cell death in insect haemocytes was also caused by several species of *Xenorhabdus* such as *X. nematophila, X. beddingii*, *X. japonica,* and *X. kozodoii* (Cho and Kim 2004).

Another cytotoxic protein CyA produced from *X. nematophila* can destroy the insects within one or two days (Khush et al. 2002). It was reported that toxin complexes of *X. nematophilus* include three insecticidal proteins $xptA_2$, $xptB_1$, and $xptC_1$ that united to form a tetramer (~1120 kDa) that attached to the outer membranes of insects and form pores in the membrane and have very high insecticidal activity against lepidopteran insects (Sheets et al. 2011). PMFI296 genes of *X. nematophila* produce insect killing proteins such as $xptA_1$, $xptA_2$, $xptB_1$and $xptC_1$. These proteins are highly virulent against *Pieris brassicae*, *P. rapae*, and *Heliothis virescens* (Sergeant et al. 2003). TccC1 toxic gene from *X. nematophila* is responsible for causing mortality in *G. mellonella* larvae (Lee et al. 2004). *X. nematophila* strain CBNU produces Txp40 protein which is toxic against larval stage of *Plutella xylostella* (Park et al. 2004). The leucine responsive protein (lrp) from *X. nematophila,* also possessed insect killing ability (Hussa et al. 2015). Xenocyloins produced from *X. bovienii* (SS-2004) also found virulent against insects and affect the haemocytic activity of insects (Proschak et al. 2014). Outer membrane vesicles (OMV) proteins GroEL homolog (~58-kDa) of *X. nematophila* also exhibit oral toxicity against *Helicoverpa armigera* (Hb.) larvae (Joshi et al. 2008). Xenematide peptides isolated from *X. nematophila* also showed insect killing potential (Lang et al. 2008). Compounds xenematides and rhabdopeptides derived from *X. nematophila* also possess insecticidal activities as they affect the haemocytes of insects (Reimer et al. 2009). Srf ABC toxin derived from the fosmid clones of *X. stockiae* HN_xs01 strain also has insect killing properties. Srf ABC toxin brings G2/M at halt and causes necrobiosis or cell death in CF-203 cells (midgut cells) of *H. armigera* larvae (Yang et al. 2019). Chitinase protein (76-kDa) from *X. nematophila* strain ATCC 19061 exhibit endochitinase activity, β-N-acetylglucosaminidase and chitobiosidase activities were found highly lethal against *H. armigera* (Mahmood et al. 2020).

Four major categories of toxin complexes are recognized such as: the *Photorhabdus* insect-related (Pir) proteins, toxin complexes (Tcs), make caterpillars' floppy (Mcf) toxins and *Photorhabdus* virulence cassettes (PVC) from *Photorhabdus*. Pir-AB toxic proteins found from the

P. luminescens TT01 genome possess insecticidal properties. The toxic proteins were effective against insect pests (Duchaud et al. 2003) as they acts as binary toxin (Yang et al. 2019) and shows resemblance with δ-endotoxins of *Bacillus thuringiensis*. Toxin complexes include numerous subunits having high molecular weight that shows insecticidal properties (ffrench-Constant 2007). Genomic study of *P. luminescens* W14 elucidate the availability of *tc* loci and cytolytic RTX-like toxins that shows resemblance with the toxins of *Erwinia chrysanthemi, Vibrio cholera, Erwinia tarda* and *Serratia marcescens* (ffrench-Constant et al. 2000). The four complexes encoded are tca, tcb, tcc, and tcd present on different locus and producing variety of compounds (Sheets and Aktories 2016). Oral toxicity by tca and tcd toxic complexes was reported in *Manduca sexta*, and these complexes were regarded as latent substitute of transgenic *Bt* formation (Bowen et al. 1998).

Even the cell-free filtrate of *Photorhabdus* spp. also exhibits insect killing properties. The genome of *Photorhabdus laumondii* (TT01 strain) encodes for a wide range of metabolic compounds including lipases, toxins, adhesins, proteases, and haemolysins and variety of antibiotic substances (Zamora-Lagos et al. 2018). Crude extract of *P. luminescence laumondii* (TT01strain) reported to cause toxicity in *Bemisia tabaci* (Shrestha and Lee 2012) and crude extract of *P. luminescence sonorensis* was effective against *Helicoverpa zea.* Many secondary metabolites produced by *Photorhabdus* also pathogenic to insects. These metabolites are anthraquinone derivatives, stilbene derivatives and genistine that are highly virulent against insects (Chalabaev et al. 2008). Anthraquinone derivatives 3-methoxychrysazine and 1,3-dimethoxy-8-hydroxy- 9,10-anthraquinone, extracted from *P. temperata* effective against various mosquito spp. (Ahn et al. 2013). Baur et al. (1998) also describe that these anthraquinone acts as an obstacle for ants and birds. Stilbenes derived from *Photorhabdus* hamper the activity of phenoloxidase by interfering and interrupting the insect (*Manduca sexta*) immune system. This phenoloxidase is the major component of insect immune system and is responsible for melanisation (Eleftherianos and Revenis 2011). TccC3 (adenosine diphosphate (ADP)–ribosyltransferases) and TccC5 (DP-ribosylated Rho guanosine triphosphatase) toxic proteins produced by *P. luminescens* hinder the mechanism of phagocytosis in insect cells and intracellular actin polymerization (Lang et al. 2010). *P. luminescens,* also produces tyrosine based compounds, rhabduscin that suppress the insect immune system (Crawford et al. 2012).

Photorhabdus temperata M1021 releases benzaldehyde, a lethal compound that acts upon the insect immune system and kill their insect hosts by seizing their immune responses in *G. mellonella.* Additionally, benzaldehyde also reduces the phenoloxidase activities and melanisation (Ullah et al. 2014). Cell-free filtrate and suspensions culture of *Xenorhabdus* spp. were found highly effective against *Hopila philanthus* (scarabaeid beetles) (Ansari et al. 2003), *Otiorhynchus sulcatus* (vine weevil), *Spodoptera exigua* (beet armyworm), *Schistocerca gregaria* (desert locust) (Mahar et al. 2008), *Tribolium castaneum* (Red flour beetle) (Shrestha and Kim 2010), *Thrips tabaci* (onion thrips), *Frankliniella occidentalis* (western flower thrips) (Gerritsen et al. 2005), *Plutella xylostella* (diamond back moth) (Mahar et al. 2008) and *G. mellonella* (greater wax moth) (Mahar et al. 2004) under the laboratory bioassay study. *X. nematophila* and *P. luminescens* were also used against *Luciaphorus perniciosus* and are highly lethal (Bussaman et al. 2012). *Xenorhabdus* and *Photorhabdus* strains possess *txp40* gene that produce ubiquitous insect killing proteins and is effective against the insect larvae belonging to order Diptera and Lepidoptera. They affect the midgut and cause injury in the fat bodies (Brown et al. 2006). Even *Xenorhabdus stockiae, X. indica, P. luminescence* subsp. *hainanensis* and *P. luminescence* subsp. *akhurstii* also cause mortality in the mosquito larvae (*Aedes albopictus* and *Aedes aegypti*) (da Silva et al. 2020).

Antibacterial activity

Endosymbionts *Xenorhabdus* spp. and *Photorhabdus* spp. exhibit antibacterial properties. The endosymbionts directly interfere in the development of the target bacteria by multiple targets systems such as biosynthesis of bacterial protein and cell-wall, DNA replication and repair system, via membrane destruction, and by metabolic pathway that ultimately inhibit the growth of the target bacteria. Leucine responsive protein (lrp) produced from *X. nematophila* showed bactericidal activities towards *Bacillus subtilis* and *Micrococcus luteus* (Cowles et al. 2007). Paul et al. (1981) reported that *Xenorhabdus* spp. secreted several metabolites having antibacterial properties. Xenocoumacin (xcnKL strain), ngrA-derived compound from *Xenorhabdus* spp. has widely adapted as antimicrobial and antibacterial properties (Singh et al. 2021). Xenocoumacin II and nematophin isolated from *X. nematophilus* possess modest antibacterial activities (Lang et al. 2008). Amicoumacin and xenocoumacin derived from *Xenorhabdus* showed a strong inhibition towards *Staphylococcus aureus* (Reimer et al. 2009). Antibiotic complexes were also reported from the genus *Photorhabdus.* Anthraquinone and trans-stilbenes were the antibacterial complexes discovered from *P. temperata* and *P. luminescens* (Boemare and Akhurst 2006). A monoterpenoid compound *trans*-4-phenyl-3-buten-2-one (benzylideneacetone) isolated from *X. nematophila*

show their potential effect against phytopathogen *Agrobacterium vitis*, *Pseudomonas syringae*, *Pectobacterium carotovorum*, *Ralstonia solanacearum,* and *P. carotovorum* (Ji et al. 2004). A lysine-rich cyclolipopetide (PAX -peptide-antimicrobial-*Xenorhabdus*) from *X. nematophila* shows modest activity against several bacteria (Gualtieri et al. 2009). Several other bioactive compounds such as indole derivatives (Sundar and Chang 1993), benzylideneacetone (Ji et al. 2004), ribosomal-encoded bacteriocins (Singh and Banerjee 2008), PAX peptides (Fuchs et al. 2011), xenocoumacins (Reimer and Bode 2014), and depsipeptides (Kronenwerth et al. 2014) were purified from *Xenorhabdus* spp.

Photorhabdus spp. released an array of secondary metabolites with a broad range of antibiotic properties that hinder the decaying of insect cadaver (Stock et al. 2017). Antibacterial capacity of *P. luminescens* was also revealed in the previous studies. Poinar Jr et al. (1980) demonstrated that *P. luminescens* hinder the development of the *B. subtilis* and *Bacillus cereus.* They were reported effective against phytopathogen *Erwinia carotovora* (Akhurst 1982a). Paul et al. (1981) reported two compounds, complex V (3,5-dihydroxy4-isopropyl-transstilbene) and complex VI (3,5- dihydroxy-4-ethyl-transstilbene) derived from *P. luminescens* showing antibiotic actions. Antibiotic effect of *Photorhabdus* spp. against *B. subtilis* was also reported by Chen et al. (1996) 1,2-isopropyl-5-(3- phenyl-oxiranyl)-benzene-1,3-diol (syn. 2-Isopropyl-5-(3- phenyl-2-oxiranyl)-1,3-benzenediol), a new antibacterial complex was also recorded from *P. luminescens* that exhibit potent bactericidal activities (Hu et al. 2006). A carbapen complex (1-carbapen-2-em-3-carboxylic acid) secreted by *Photorhabdus* represent insecticidal potential against various bacterial species including *Klebsiella pneumonia, Enterobacter cloacae,* and *Escherichia coli* (Derzelle et al. 2002).

Anthraquinone by products 1,8-dihydroxy3-methoxy-9,10-anthraquinone and 3,8-dihydroxy-1-methoxy-9,10-anthraquinone derived from Type II polyketide synthase enzymes of *Photorhabdus* shows antibacterial activities (Challinor and Bode 2015). Bactericidal effect of *Photorhabdus luminescens* subsp. *akhurstii* (bSBR36.2_TH) was reported against *E. coli*, *Bacillus subtilis*, *S. aureus* RN4220, and *S. pyogenes* (Derzelle et al. 2002). *P. luminescens* produces photobactin (2-(2, 3-dihydroxyphenyl)-5-methyl-4, 5-dihydro-oxazole-4-carboxylic acid [4-(2,3-dihydroxybenzoylamino)-butyl]-amide) a catecholate siderophore that shows antibiosis against insects (Ciche et al. 2003). Bactericidal activities of *Photorhabdus* spp. were effective against Gram negative bacteria *Erwinia amylovora* responsible for causing fire blight in rosaceae (Hevesi et al. 2004) and manage two more bacterial spp. *Xanthomonas* and *Pseudomonas* in plants (Uma et al. 2010). Numerous biological activities including bactericidal activities were observed from isopropylstilbene compound produced by *Photorhabdus* spp. against *S. aureus* and *E. coli* (Shi et al. 2017). Muangpat et al. (2017) emphasized the bactericidal properties of *Photorhabdus* spp. The growths of about 10 drug-resistant bacterial strains together with *S. aureus* strain PB57, PB36 and ATCC20475 prohibited by the extract (ethyl acetate) of *P. temperata.* Bacterial spp. *P. luminescence* subsp. *akhurstii* was recorded to effectively suppress the *S. aureus* strain PB36 (Muangpat et al. 2020).

Antifungal activity

The metabolites produced by endosymbionts have been reported to inhibit the growth of the multiple fungi. Huge numbers of research studies were carried out and being continued to measure the efficacy of endosymbionts against fungal pathogens. *X. nematophila* produces cyclolipopetide having lysin rich residue is highly effective against fungal pathogens including plant as well as animal fungal pathogens (Gualtieri et al. 2009). Chen et al. (1994) evaluated the inhibitory effect of *X. nematophilus X. bovienii* and *P. luminescens* against 32 fungal species and they found effectiveness against all fungal species. Even the growth of 7 major phytopathogenic fungi: *Trichoderma pseudokingi, Botrytis cinerea*, *Mucor piriformis*, *Ceratocystis ulmi*, *Pythium coloratum*, *Ceratocystis dryocoetidis*, and *Pythium ultimum* were completely suppressed by these endosymbionts. Webster et al. (1995) reported the fungicidal activities of endosymbionts *Xenorhabdus* and *Photorhabdus.* The metabolic complexes from *Xenorhabdus* and *Photorhabdus* were isolated and it is found that these compounds have defensive and fungus eliminating properties. High antimycotic effect was recorded in *Sclerotinia sclerotiorum* when cell free filtrate of *X. szentirmaii* was applied (Chacon-Orozco et al. 2020). It was reported that inside insect cadaver antimycotic substances were produced by *Photorhabdus* spp. that protect the cadaver and prevent the growth from invading fungal pathogen (Chen et al. 1994). Crude extract of *Photorhabdus* spp. was assessed against fungal phytopathogens such as *Phomopsis* sp., *Fusi cladosporium effusum*, *Glomerella cingulata, Phytophthora cactorum,* and *Monilinia fructicola.* Modest effect of endosymbionts against fungal phytopathogens was observed (Shapiro-Ilan et al. 2009). Strong fungicidal effect of *Photorhabdus* spp. was observed towards *Moniliophthora roreri* (San-Blas et al. 2012). Even several specified secondary metabolic complexes have been applied to assess their antimycotic peoperties. Li et al. (1995b) applied 3,5-dihydroxy-4-isopropylstilbene on

fungi *Aspergillus fumigatus*, *A. flavus*, *Cryptococcus neoformans, Botrytis cinerea*, and *Candida tropicale*.

Photorhabdus temperata SN259 strain produces seven metabolic complexes among which two stilbene complexes such as 3-hydroxy-2-isopropyl-5-phenethyl phenyl carbamate and 2-isopropyl-5-([E]-2-phenylethenyl) benzene-1,3-diol (syn. 3,5-dihydroxy-4-isopropyl stilbene) were applied to investigate its impact upon *F. oxysporum, Rhizoctonia solani*, *Pythium aphanidermatum,* and *Exserohilum turcicum.* A highly strong inhibitory effect has been observed against *P. aphanidermatum* (Shi et al. 2012). Transcinnamic acid isolated from *P. luminescens* prevents the growth of the *Fusicladium effusum* (Bock et al. 2014). *P. temperata* M102 derived metabolite benzaldehyde was assessed against three phytopathogens *Phytophthora capsici, Corynespora cassiicola,* and *R. solani.* Benzaldehyde shows high inhibitory effect against the fungal phytopathogen. Even *Photorhabdus* spp. has been reported to hinder the growth of about 32 fungal species (Ullah et al. 2014). Trans-cinnamic acid (TCA) isolated from *Photorhabdus* sp. hinder the growth of *Colletotrichum acutatum*, *Colletotrichum gloeosporioides* and *Colletotrichum fragariae* (Chen et al. 1996). TCA also inhibits the growth of *F. effusum* (Shapiro-Ilan et al. 2014). The efficiency of cell free filtrate from *P. luminescens* strain VS, *P. temperata* and *P. luminescens* strain K122 was assessed against various phytopathogenic fungal species such as: *Armillaria tabescens, Fusicladium carpophilum, F. effusum, Glomerella cingulata* and *Monilinia fructicola*. It was found that these supernatants completely suppress the growth of the phytopathogenic fungi (Hazir et al. 2016). Under an in vitro inhibition test, fungi *Alternaria alternate* and *Fusarium oxysporum* sp. *asparagi* were treated with the crude extract of *P. luminescens* sp. *sonorensis,* that show mild effect against these fungi although the growth was retarded (Orozco et al. 2016). Secondary metabolic complexes produce by *P. akhurstii* exhibit fungicidal activities against *Colletotrichum gloeosporioides* (Tu et al. 2022).

Nematicidal activity

The cell free substrate of *Photorhabdus* spp. not only exhibit insecticidal, antibiotic and antimycotic activities but also possesses nematicidal properties. They have been reported to kill or manage various species of plant parasitic nematodes. Several strains of *Photorhabdus* spp. were evaluated against *Meloidogyne incognita* and *Bursaphelenchus xylophilus*. They were highly lethal against second-stage juveniles of *M. incognita* and adults as well as fourth-stage juveniles of *Bursaphelenchus xylophilus* (Hu et al. 1999). Crude extract of *P. luminescens sonorensis* CH35 strain was applied against three nematode species namely: *M. incognita, Caenorhabditis elegans* and *S. carpocapsae*. It was found that this supernatant was highly effective against *M. incognita* (J2), while it exhibited very low nematicidal activities against *C. elegans* and *S. carpocapsae* (Orozco et al. 2016). The metabolic substances stilbene (3,5-Dihydroxy-4-isopropylstilbene) and indole produced through *P. luminescens* strain MD were tested against *Aphelenchoides rhytium, Bursaphelenchus* spp., *C. elegans* and *M. incognita.* High nematode killing abilities were exhibited by these derivatives against fourth-stage juvenile and adult forms of three tested species; however, no nematicidal effect of these metabolites has been observed against *M. incognita* (J2) (Hu et al. 1999). Cell-free supernatant of *Xenorhabdus* spp. is highly toxic against *M. incognita* and showed inhibitory effects (Grewal et al. 1999). Lewis et al. (2001) worked on the interactions of *S. feltiae* and *X. bovienii* with *M. incognita* and found that tomato plant infected with *M. incognita* when treated with same rate of *S. feltiae,* affect egg production with lesser galls in their roots. *X. bovienii* also shows inhibitory effect against *M. incognita.*

Cell-free filtrate of *X. bovienii* was applied against *Meloidogyne javanica* and *M. incognita* and a moderate effect was observed (Kepenekci et al. 2018). Bi et al. (2018) reported about seven metabolites (Rhabdopeptide I-O or 1–7) from *X. budapestensis* SN84 that possess nematode killing properties and is found effective against *M. incognita* (J2). Among all seven isolated metabolites, rhabdopeptide J2 was highly effective. *Xenorhabdus* spp. along with neem cake and furadan was applied to control the *M. incognita* infestation in Grapevines. It was reported that all treatment significantly suppresses the nematodes population in grapevines (El-Deen et al. 2019).

Bioformulations produced from endosymbionts

Bioformulations are biological pesticides invented with useful microbiomes including bacteria, viruses, fungi, nematodes, and plant-based extracts as well as semiochemicals, as active component. Generally, bioformulations developments are based upon the bioresource detection, optimization, stabilization, and risk executive energy. The biopesticides have been regarded as best alternate of chemical insecticides in sustainable crop production due to their eco-friendly behaviour (Gašić and Tanović 2013). Nowadays, peoples become aware about the hazards caused by extensive use of synthetic chemical insecticides and moving towards healthy and organic foodstuff. Bioformulation applications easily tackle the insect resistance problems, provide effective protection to the crops and are an important part of integrated pest management (IPM) strategies (Elad et al. 1996). A wide range of biopesticides from entomopathogenic bacteria were available for insect pest management. These

formulations are in the form of dry (granular) and wet products (liquid and wet powder) (Singh et al. 2014). Dust powder, seed dressing powder, water dispersible granules as well as wet powders form with dilution attributes are considered under dry formulations. Emulsions, suspoemulsions, suspension concentrates, capsule suspensions, oil dispersions, and ultra-low-volume formulations were considered under wet products/formulation (Knowles 2005). The endosymbionts *Xenorhabdus* and *Photorhabdus* exhibited insecticidal, antimycotic, bactericidal and nematicidal activities so they can be employed for bioformulation production (Namsena and Bussaman 2020). Namsena et al. (2016) reported three bioformulations of *Xenorhabdus* (*X. stockiae* PB09) in the form of liquid supernatant, cell pellet, wettable powder form and observed high mortality in mites even after storage up to 45 days at 4 °C. *P. luminescens* along with paraffin oil, Tween-20 and sucrose were applied directly as a spray against *Pieris brassicae*, and 100% larval mortality was observed within 24 h of foliar application (Mohan et al. 2003). Sodium alginate capsules were also prepared from *P. luminescens akhurstii* that was reported to cause 100% killing of *S. litura* within 48 h of its infection (Rajagopal et al. 2006). Toxicity in *Prays oleae* was also recorded by *P. temperate,* when ingested directly (Tounsi et al. 2006) (Fig. 3).

Conclusion and future prospects

Entomopathogenic nematodes (EPNs), the valuable nematodes, have been reported as the finest biocontrol agents. EPNs are considered as the best substitute of chemical insecticides due to their high potential of infecting the insects hidden even in mysterious places with high multiplication ability as well as their eco-friendly nature. In the field of biological pest management, the application of EPNs along with their bacterial symbionts becomes a popular approach of pest control. The diversified secretion systems of entomopathogenic bacteria were involved in the release secondary metabolite. These secondary metabolites are toxic proteins that possess high insecticidal potential along with high antimicrobial activities. *Xenorhabdus* and *Photorhabdus* strains produced multiple metabolites that act against a variety of organisms including, protozoans, fungi, nematodes

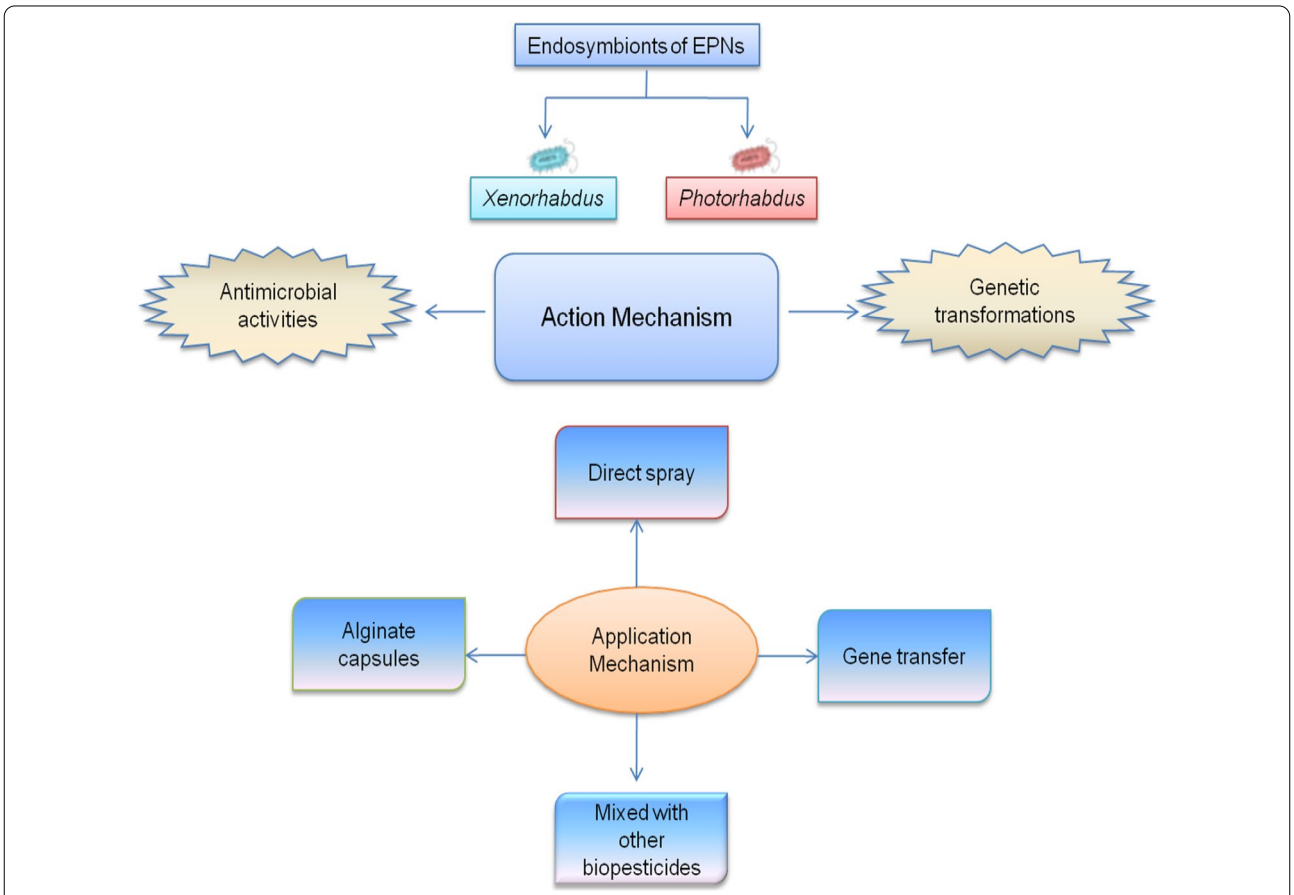

Fig. 3 Application strategies for bacterial endosymbionts

insects, and even against cancerous cells. Various kinds of antibiotic were also produced from several species of symbiotic bacteria that showed the importance of these bacterial symbionts in the drug industry. There is a need of more surveys on EPNs to discover more species of endosymbiotic bacteria. The secondary metabolites, rich sources of toxic and bioactive compounds from endosymbiotic bacteria, need to be optimized and explored in the future; along with that there is a necessity of development of some by-product from these bacteria and their metabolites.

Abbreviations
X. nematophila: *Xenorhabdus nematophila*; *P. luminescens*: *Photorhabdus luminescens*; IJs: Infective juveniles; EPNs: Entomopathogenic nematodes; BCAs: Biocontrol agents; %: Percent.

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Author details
[1]Department of Zoology, Akal College of Basic Sciences, Eternal University, Sirmour 173101, India. [2]Department of Biotechnology, Dr. Khem Singh Gill Akal College of Agriculture, Eternal University, Sirmour 173101, India.

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