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Physiological and Biochemical Disturbances in the Insect Pests Infected with Entomopathogenic Nematodes: A comprehensive review

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ABSTRACT

The excessive and indiscriminate uses of synthetic chemical insecticides have led to many serious problems of human health, ecosystem and economics. Therefore, it is necessary to search for safe and eco-friendly alternatives. Among these promising alternatives is the use of entomopathogenic nematodes (EPNs) for pest control. The objective of the present review was to give an insight into some of the physiological and biochemical disturbances in insects due to the infection with EPNs. Therefore, the current article discussed (1) the impaired intermediary metabolism including the main body metabolites (proteins, lipids and carbohydrates), and food consumption and utilization efficiencies; (2) the drastic effects of EPNs on some developmental and reproductive criteria of the insects; (3) the disrupted activities of major digestive enzymes including carbohydrate, protein and lipid hydrolyzing enzymes; (4) the disturbing effects of EPNs on the detoxification enzymes and the major humoral immunity-related enzymes. The disruptive effects of the EPNs on insects have suggested the potential of these entomopathogens for pest control. To the best of our knowledge, this is the first comprehensive review for understanding the principal physiological and biochemical mechanisms involved in the insects to combat the EPN oxidative stress. The current review will no doubt suggest new research avenues to many investigators, and it will make a valuable contribution to the published literature. However, some points of research need more investigation in future, such as the link between humoral immunity defenses and cellular immunity defenses to understand the defense integration in insects against EPNs.

Contents:

INTRODUCTION

Although the integrated pest management (IPM)strategies are increasingly developed in different parts of the world (Veres *et al*., 2020), the control of insect pests still relies mainly on application of the synthetic insecticides (Jeschke *et al*., 2011; Meslin *et al*., 2021). The intensive and indiscriminate uses of these chemicalshave led to negative impacts on the ecosystems including water, air and soil pollution (Tiryaki and Temur, 2010; Gunstone *et al*., 2021) and drastically affect the natural enemies (like parasites and predators) leading to outbreaks of the pest populations (Demok *et al*., 2019) as well as adverse effects on domestic animals (Vattikonda and Sangam, 2017; Shahzad *et al*., 2020). Acute or chronic illnesses can develop in people who have been exposed to insecticides, either directly or indirectly (Mostafalou and Abdollahi, 2012). Additionally, conventional pesticides have serious impacts on both target and non-target organisms including birds, fish, amphibians, earthworms, and pollinators (Gill and Garg, 2014). InEgypt, as for example, the controlof cutworms depends mainly on the application of conventional insecticides (Vattikonda and Sangam, 2017; Ismail, 2021). Some authors reported that the chemical control for these pests is often ineffective and remains inadequate because of the larval hiding behavior during the daylight hours causing hidden damage in fields (Capinera, 2001; Takeda, 2008, Kumar *et al*., 2022), besides the fast development of resistance and cross resistance to almost all marketed insecticides (Yu Dong *et al*., 2012; Mahmoud *et al*., 2016;Shaurub *et al*., 2018).

Therefore, various research institutions in the world have searched for new control agents as alternatives to synthetic insecticides (Laznik and Trdan, 2012; Derbalah *et al*., 2014; Glare *et al*., 2016). These alternative agents should be eco-environmentally safe (Liao *et al*., 2017; Kunbhar*et al*., 2018), effective at low concentrations (Walkowiak *et al*., 2015) and biodegradable into harmless compounds (Tiryaki and Temur, 2010; Li *et al*., 2017). One of these alternatives is the biocontrol of insect pests using natural enemies (parasitoids, predators and pathogens). Biocontrol agents are highly promising (Amutha *et al*., 2021) because they are safe for humans and the environment, as well as they have little or no effect on other non-targeted organisms (Jagodič *et al*., 2019).

Among the biocontrol agents, entomopathogenic nematodes (EPNs) have broad potential to kill the soil-dwelling insect pests as well as the above-ground insects which have soil-dwelling stages (Laznik and Trdan, 2011; Lacey and Georgis, 2012; James *et al*., 2018; Du Preez *et al*., 2021a, b; Kumar *et al*., 2022). Moreover, various EPNs species are now applied against a wide range of foliar pests occurring in different habitats (Brusselman*et al*., 2012; *Beck et al*., 2013; Mahmoud, 2014; Gözel and Gozel, 2016). For example, EPNs *Steinernema carpocapsae* and *Heterorhabditis indica* possess significant potential for controlling several insect pests (Sunanda *et al*., 2014; Khan *et al*., 2018; Viteri *et al*., 2018).

Distribution, virulence, and usage of EPNs in IPM programs have been studied globally (Çağlayan *et al*., 2021; Ali *et al*., 2022) because they are harmless to non-target organisms, human health and the environment (Odendaal *et al*., 2016; Gulcu*et al*., 2017; Kumar *et al*., 2022; Peçen and Kepenekci, 2022). Also, EPNs have high reproductive potential, the ability to kill hosts quickly, high virulence, broad host range, and safety to plants and vertebrates (Kaya and Gaugler, 1993). Most biocontrol agents require days or weeks to kill the insect pests, yet EPNs, working with their symbiotic bacteria, kill insects in 24-72 h (Adams and Nguyen, 2002). In addition, EPNs can be easily mass produced and applied using common irrigation and pesticide equipment (Askary and Abd-Elgawad, 2021; Yağci *et al*., 2021a,b).

As biocontrol agents, EPNs can be used individually or in combination with other entomopathogenic bacteria or fungi in order to improve their efficacy for controlling the insect pests (Krishnayya and Grewal, 2002; Laznik *et al*., 2012; Amizadeh*et al*., 2019). Also, EPNs were found compatibile with different agrochemicals (for review, see Ghoneim and Hamadah, 2024). EPNs have a high tolerance to the variations in environmental conditions (Toledo *et al*., 2010). For some details, see Vashisth *et al*. (2013), Sujatha and Jeyasankar (2018), Jagodič *et al*. (2019), Askary and Abd-Elgawad (2021), Kumar *et al*. (2022**)**, Shaurub **(**2023) and Ghoneim and Hassan, 2024).

It is important to point out that the EPNs parasitism leads to the suppression of the immune system of the insect host (Lewis and Clarke, 2012; Shapiro-Ilan and Brown, 2013; Lacey *et al*., 2015; Kaliaskar*et al*., 2022). Moreover, EPNs have an association with certain symbiotic bacteria which are carried in the intestine of infective juveniles (IJs) of EPNs (Arthurs *et al*., 2004; Lewis and Clarke, 2012; Chaston *et al*., 2013). Among 23 families of EPNs, Steinernematidae and Heterorhabditidae are the two most potential families living naturally in the soil (Kumar *et al*., 2015) and used as biocontrol agents against many insect pests (Lacey and Georgis, 2012; Abd-Elgawad, 2020; Koppenhöferet *al*., 2020; Yüksel *et al*., 2022). Their association with symbiotic bacteria is found to be the primary cause of insect mortality (Leonar*et al.*, 2022). Symbiotic bacteria of the genera *Xenorhabdus* and *Photorhabdus* associate with the EPN families, Steinernematidae and Heterorhabditidae, respectively, which produce natural products with insecticidal potential (Vicente-Díez *et al*., 2021) for the suppression of the immune system of the insect host (for more detail, see Lewis and Clarke, 2012; Shapiro-Ilan and Brown, 2013; Lacey *et al*., 2015; Koppenhöfer*et al*., 2020; Bhat *et al*., 2020; Kaliaskar*et al*., 2022;Ghoneim,2024).

In this context, the pathogenicity of EPNs begins immediately after entering the insect's haemocoel where they release their symbiotic bacteria and rapidly multiply causing lethal septicemia to the insect host (Nickle and Welch, 1984). Also, the success of entomopathogens for the insect control depends on their stress potential and capability to impair certain physiological processes and biochemical constituents of the insect hosts. Over the past two decades, there has been increasing evidence that some EPNs influenced certain metabolic processes (Shaurub*et al*., 2020; Ghoneim *et al*., 2022) and some important enzymatic activities (Abdel-Razek *et al*., 2004; Shaurub*et al*., 2015; Ibrahim *et al*., 2015; Shairra*et al*., 2016; Vidhya *et al*., 2016; Ghoneim *et al*., 2023a).

On the other hand, haemolymph is the only extracellular fluid in the insect body that is usually circulated by an open system within the body cavity. It performs several functions, such as the transportation of food materials to the cells and metabolic waste products away from those cells. It,also, transports hormones for regulation of larval moulting, growth, metamorphosis, metabolism and other physiological processes of insects (Hietakangas and Cohen, 2009). In insects, the use of haemolymph as a medium for controlling insect pests has been investigated because the changes occurring in the haemolymph are quickly transferred to other portions of the insect's body (Rodriguez-Ortega *et al*., 2003; Pugazhvendan and Soundararajan, 2009). Therefore, physiological and biochemical disturbances in the haemolymph are expected, since the haemolymph is the main site of action of invading EPNs (Ghoneim *et al*., 2022, 2023a).

Some attempts have been made to understand the principal physiological and biochemical mechanisms involved in the insect infection. Therefore, objective of the **present review** was to give an insight into the physiological and biochemical disturbances in the insect hosts, post-infection with EPNs, including impaired intermediary metabolism, disrupted developmental and reproductive processes, disturbed digestive enzymes, detoxifying enzymes and the major humoral immunity-related enzymes.

1. Impaired Intermediary Metabolism of Insect Pests by EPNs:

1.1. Disrupted Main Body Metabolites in Insects by EPNs:

In insects, different biological and physiological processes need adequate energy (Chapman, 1998; Fagan et al., 2002). The content of macromolecules (such as protein, lipid and carbohydrate) is a valuable indicator of the level of metabolism, after treatment with exogenous materials (Zhu *et al*., 2012). It is important to mention that protein synthesis is crucial for insect development and reproduction. Carbohydrates are the main source of energy during insect metamorphosis. Energy reserves, such as proteins, lipids, and glycogen in the haemolymph, are also an important indicator of the level of metabolism in insects (Chowanski*et al*., 2015; Ferreira *et al*., 2014; Ismail, 2018). These energy reserves are closely related to different physiological and biochemical processes in insects (Nawaz *et al*., 2017).

1.1.1. Disruptive Effects of EPNs on the Protein Content in Insects:

Proteins are important organic constituents of animal tissues, including insects, and they play an important role in energy production (Taşkın and Aksoylar, 2011). The protein synthesis in insects is a prerequisite process for the development and reproduction (Hahn and Denlinger, 2007; Taşkın and Aksoylar, 2011). As reported by several authors (Suarez et al., 2005; Bernstein and Jervis, 2008; Sugumaran, 2010), proteins perform a wide variety of physiological and metabolic functions and play a key role in the production of microsomal detoxifying enzymes.

Based on the available literature, the total protein content in the haemolymph of 4th instar of the mosquito *Culex pipiens* (Diptera: Culicidae) was reduced after infection with the EPN *Romanomermisculicivorax* (Schmidt and Platzer, 1980). The haemolymph protein content of the Egyptian cotton leafworm *Spodoptera littoralis* (Lepidoptera: Noctuidae) larvae was markedly reduced 30 hrs post-infection with some EPNs (El-Bishry, 1989). Also,

the total proteincontent of *S. littoralis* larvae was significantly reduced after infection with the EPNs *Steinernema riobrave* and *Heterorhabditisbacteriophora* (Ahmed et al., 2014). Four EPNs *H. bacteriophora* AS1, *H. bacteriophora* HP88, *Steinernema carpocapsae* ALL, and *S. riobrave* ML29 caused a remarkable decline in the total protein content of larvae of the Mediterranean fruit fly *Ceratitis capitata* (Diptera: Tephritidae) (Shaurub et al., 2015).

In Egypt, also, Hassan *et al*. (2016) studied the disturbance of protein contentin 6th instar larvae of the black cutworm *Agrotisipsilon* (Lepidoptera: Noctuidae) at different time intervals after infection with *S. glaseri* and *H. bacteriophora*. They determined a significant reduction in total protein content 24 hr post-infection. Two years later, infection of 5th instar nymphs of the desert locust *Schistocerca gregaria* (Orthoptera: Acrididae) with 1000 and 2000 IJs of *H. bacteriophora* resulted in reduction of the total protein content in nymphs (Gaber *et al*., 2018). Shaurub*et al.* (2020) incubated the newly moulted 4th instar larvae of *S. littoralis* with LD_{50} of EPNs *Steinernema riobrave* and *H. bacteriophora* for 24 h. They determined decreasing protein content in the infected larvae. Also, Gomaa *et al*. (2020) evaluated the efficacy of two EPN isolates (*H. bacteriophora* and *S. carpocapsae*) and the Entomopathogenic fungus *Beauveria bassiana*, separately and in combination, on the 3rd instar larvae of *S. littoralis*. According to their results, total protein content was reduced post-infection with all treatments. In a recent study conducted in Egypt byGhoneim *et al*. (2022), a predominant reduction of the protein content in haemolymph of last instar larvae of *A. ipsilon* was determined after infection with *S. carpocapsae* and *H. bacteriophora*. Moreover, *H. bacteriophora*exhibited stronger reducing potency against the protein content than *S. carpocapsae*, at 48 h post-infection (See Table 1).

Table 1. Total protein content inhaemolymph (g/dL) of last (6th) instar larvae of *Agrotisipsilon* as influenced by treatment of the newly moulted 5th instar larvae with LC_{50} values of the tested entomopathogenic nematodes.

Nematode species		Time interval		
		6 hr	24 hr	48 hr
S. carpocapsae	mean±SD	6.10±0.12 a	5.78±0.33 a	4.84±0.12 b
	Change (%)	-13.84	-9.26	-21.94
H. bacteriophora	mean±SD	5.75±0.59 a	5.47±0.55 a	4.56±0.37 b
	Change (%)	-18.78	-14.12	-26.45
Control	mean±SD	7.08±0.84	6.37±1.21	6.20±0.49

Mean ± SD followed with letter: a: insignificant (P >0.05), b: significant (P<0.05), c: highly significant (P<0.01), d: very highly significant (P<0.001) (After Ghoneim *et al*., 2022).

In contrast, the current literature contains, also, few reported results of increasing protein content in larvae of some insects after infection with certain ENPs, such as *C. capitata* larvae at 4 and 18 h post-infection with *S. feltiae*Filipjev (Ghally*et al*., 1988). Also, total protein content significantly increased in the full-grown larvae of pink bollworm *Pectinophoragossypiella* (Lepidoptera: Gelechiidae) after treatment with *S. riobrave* but slightly increased after infection with *H. bacteriophora* (Shairra*et al*., 2016). Infection of the 5th instar nymphs of *S. gregaria* with the concentrations 1000 and 2000 IJs of *H. bacteriophora* resulted in disturbance of total protein contents in nymphs (Gaber *et al*., 2018).

Reduction of proteins in haemolymph of insects after infection with some EPNs may be attributed to the proteolytic activity in the haemolymph of the infected larvae. This activity was suggested to be the main cause of the host quick death (El-Bishry, 1989). According to some authors (von Brando, 1973; Lee and Atkinson, 1976), the considerable reduction of protein content may occur because many EPNs secrete chemicals (including toxins and digestive enzymes) to facilitate penetration and migration through the host tissues, and for feeding and avoiding the host immune responses. More than two decades later, some authors

(Istkhar and Chaubey, 2019; Wee et al., 2000) suggested that the production of proteases by EPN-symbiotic bacterial cells, followed by the breakdown of insect's protein and serving as nutritional resources for EPN/bacterium development. Also, reduction of proteins after infection with EPNs may be due to the stimulation of protein catabolism in the host fat body- the major organ for metabolism, nutrient storage, and synthesis of vitellogenin, a yolk protein precursor (Kamruzzaman*et al*., 2020) - to acquire a dietary supply of amino nitrogen from haemolymph (Gordon *et al*., 1973).

Early, Schmidt and Platzer (1980) reported that the protein degradation, when the mosquito *Cx. pipiens*were infected with EPN *R. culicivorax* may be attributed to the production of some proteases from EPNs leading to this degradation in haemolymph. Also, the protein reduction in haemolymph might be due to the conversion of some proteins to fat, resulting in low protein content in the infected larvae (Abdel-Razek *et al*., 2004). In addition, breakdown of the proteins into free amino acids would ultimately lead to decrease in protein content. Moreover, the decreased protein content may be expected to suppress the immune response of infected larvae, including encapsulation, prophenoloxidase activity, phenoloxidase activity, total haemolymph proteins, and hemocyte density (Wilson *et al*., 2019).

1.1.2. Disruptive Effects of EPNs on the Lipid Content in Insects:

Lipids represent a principal source of energy for insects. They are transferred from their synthesis site *via* the haemolymph towards the target organs for use, in particular chitin synthesis, oogenesis, vitellogenesis, embryogenesis and continuous muscular activity (Dapporto*et al*., 2008; Zhou and Miesfeld, 2009). In addition, tothe sites of lipid storage in the body, egg lipids play a very important role for achieving energy needed for the developing embryo (Boz and Gülel, 2012). Quantity of lipids available for the reserves seems to be the result of a balance between the obtained food and the requests for reserves by processes, such as maintenance, growth and reproduction, and this balance is disturbed by any xenobiotic stress (Canavoso*et al*., 2001). Also, impaired synthesis of lipidshas been resulted in adversely influenced physiology and subsequently disrupted vital functions of growth and reproduction (Ghoneim *et al*., 2022).

Total lipids in *C. capitata* larvae declined after 18 h post-infection with *S. feltiae* (Ghally*et al*., 1988). The total lipid content of the *S. littoralis* larvae was significantly decreased post-infection with *S. riobrave* or *H. bacteriophora* (Ahmed *et al*., 2014). It was remarkably decreased in the 4th instar larvae of *S. littoralis* after incubation with LD_{50} values of *S. riobrave* or *H. bacteriophora* for 24 hr (Shaurub*et al.,***2020**). In Egypt, Ghoneim *et al*. (2022**)** obtained similar results of lipid reduction. Depending of their results, the lipid content in haemolymph of the EPN-infected *A. ipsilon* larvae was gradually reduced with age. The greatest reduction of lipids was determined in larvae at 48 h (26.55 & 21.73% lipid reduction, by *S. carpocapsae* or *H. bacteriophora*, respectively). As clearly seen, *S. carpocapsae* exerted stronger reducing action on the lipid content of infected larvae than *H. bacteriophora*. On the other hand, lipid content in the fat body of the red palm weevil *Rhynchophorus ferrugineus* (Coleoptera: Curculionidae) larvaeincreased after infection with *S. carpocapsae* or *H. bacteriophora* (Abdel-Razek *et al*., 2004). In Egypt, also, the *P. gossypiella* full-grown larvae were infected with LC_{50} of *H. bacteriophora* and *S. riobrave* by Shairra*et al*. (2016) who recorded an increase of free fatty acids.

To interpret the reduction of total lipid content in last instar larvae of different insects after infection with some EPNs, it may be important to point out that the lipid turnover in insects is regulated by neuroendocrine-controlled feed-back loops (Kim *et al*., 2002; Etebari*et al*., 2007). Therefore, the reduced lipid content might be due to the disrupting effects and stress of these EPNs on neurosecretion or other hormones in larvae. Also, the declined lipid level in larvae might be due to shift in energy metabolism towards lipid catabolism as a result

of physiological stress caused by the tested EPNs.In other words, these EPNs induced stress on larvae to uselipids and glucose for cell repair and increasing protein catabolism which may be stimulated due to high energy demand under such stress conditions.

1.1.3. Disruptive Effects of EPNs on the Carbohydrate Content in Insects:

In insects, carbohydrates represent an important energy source and perform a crucial role in the structure and function of tissues during development and metamorphosis, as well as for the maturation of reproductive organs and embryonic development (*cf*. Chippendale,1978). In insects, also, the soluble carbohydrates are accumulated during larval stage and utilized in metamorphosis (Pant and Kumar, 1979). Also, they are stored in the fat body as glycogen, which is converted into trehalose before releasing into the haemolymph for utilization (Gilbert and Chino, 1974). It is important to mention that carbohydrates can be disturbed by xenobiotics (Kaufmann and Brown, 2008).

Total carbohydrates in haemolymph of 4th instar larvae of *Cx pipiens* was reduced after infection with the EPN *R. culicivorax* (Schmidt and Platzer, 1979). Infection with the EPN *Mermis nigrescens* resulted in the decrease of trehalose level and reducedcarbohydrate metabolism in the fat body of its host, *S. gregaria* (Gordon *et al*., 1971). The total carbohydrate content of *S. littoralis* larvae was significantly decreased by post-infection with EPNs *S. riobrave* and *H. bacteriophora* (Ahmed *et al*., 2014). In Egypt, Shaurub et al. (2020) determined decreasingcarbohydrate content in the 4th instar larvae of *S. littoralis* after infection with LD_{50} of *S. riobrave* and *H. bacteriophora* for 24 h. Results obtained by Ghoneim *et al*. (2022)in Egypt were in accordance with these reported results of decreased carbohydrates in larvae of some insects after infection with certain EPNs, since carbohydrate content was prevalently reduced in haemolymph of the EPN-infected larvae of *A. ipsilon*. Also, the reducing potency of EPNs considerably increased with the time interval of exposure (41.38 and 31.03% carbohydrate reductions by *S. carpocapsae* and *H. bacteriophora*, respectively, at 48 h).

Schmidt and Platzer (1979) recorded a remarkable decline of glucose and trehalose levels in the haemolymph of 4th instar of the mosquito *Cx. pipiens*, after infection with EPN *R. culicivorax*. In contrast, *H. bacteriophora* AS1, *H. bacteriophora* HP88, *S. carpocapsae* ALL, and *S. riobrave* ML29 significantly enhanced the total glucosecontent in *C. capitata* 3rd instar larvae (Shaurub*et al*., 2015).

Reduction of carbohydrate content in haemolymph of the insect after infectionwith EPNs may result from the nematode's nutritional demands for glucose and accelerated glycogenolysis and/or impaired glycogenesis. In other words, decrease of carbohydrates indicated that more sugar may be metabolized to meet the energy demands of EPNs and the host leading to consumption of sugar and carbohydrate contents (Sharma *et al*., 2011; Yazdani *et al*., 2014; Shaurub*et al*., 2020). The interaction between EPNs and insect larvae appeared to be primarily nutritional. Growth of the EPNs proceeds while the nutritional requirements of the host larvae deteriorate resulting in a state of physiological starvation (Ahmed *et al*., 2014). On the other hand, the EPNs may interfere with the hormonal regulation of carbohydrate metabolism in larvae (Gade, 2004; Sugumaran, 2010) or exhibited some effects on the carboxylase activity (Mukherjee and Sharma, 1996).

1.2. Disrupted Food Consumption and Utilization in Insects by EPNs:

In insects, the physiological events that are linked to food consumption and utilization appear to be regulated by neural, endocrine and secretogogue mechanisms (Chapman, 1985). Hormones produced by the brain neurosecretory cells, corpora cardiaca and corpora allata also regulate the digestive enzyme production (Prabhu and Sreekumar, 1994). For instance, in last instar larvae of the lawn armyworm *Spodoptera mauritia* (Lepidoptera: Noctuidae), maximal feeding activity is attained at high Juvenile hormone (JH) titer but when JH titer

declines and the subsequent release of ecdysteroids, the feeding activity decreases (Balamani and Nair, 1992; Mona, 2001).

On the other hand, feeding and reproduction in insects are closely related to nutritional factors, the qualitative and quantitative aspects of which have impact on the growth, development and fecundity (Slansky and Scriber, 1985). Therefore, an understanding of the nutritional indices in relation to the efficacies of ingestion, digestion, assimilation and food conversion by the growing larvae would be physiologically useful (Scriber and Slansky, 1981).More than three decades later, Lazarevi and Tomani (2015) reported the importance of understanding the digestive physiology of an insect for both fundamental studies of the mechanisms and patterns of dietary specialization and applied studies searching for efficient strategies of the pest control.

In this context, the most important parameters of food consumption and utilization are Consumption index (CI), Approximate digestibility (AD), Efficiency of conversion of ingested food to body substance (ECI), Efficiency of conversion of digested food to body substance (ECD), Growth rate (GR) (Waldbauer 1968) and Assimilation rate (AR)(Scriber and Slansky, 1981). Relative metabolic rate (RMR) was calculated according to Slansky (1985). These parameters may help to determine the nutritional efficiencies which can affect growth in insects (Johnson and Mundel, 1987; Hinks *et al*., 1991).

Only, a little attention has been paid to the food consumption and utilization efficiencies in entomopathogen-infected insects (Tefera and Pringle, 2003; Hussain *et al*., 2015). To our knowledge, scarce information exists in the current literature concerning the disruptive effects of EPNs on the food consumption and utilization of insect pests. Infection of the newly moulted 4th instar larvae of *S. littoralis* with *H. bacteriophora* resulted in a decrease of CI of 2- and 3-day-old larvae (Shaurub*et al*., 2020). To understand this reduction of food consumption, IJs of EPNs penetrate the haemocoel of the insect host, they rapidly multiply, causing lethal septicaemia in the host (Wouts, 1984). Also, heterorhabditid EPNs can rupture the host cuticle (Poinar, 1990).

In addition, AD in the entire 6th instar of *S. littoralis* increased after infection of *S. littoralis* 4th instar larvae with *S. riobrave*. In contrast, infection with *H. bacteriophora* led to a decrease of AD of 2-day-old 4th instar larvae (Shaurub*et al*., 2020). As reported by Barnby and Klocke (1987), the increasing AD may be due to a higher retention of the food bolus in the gut for a longer period and thereby longer exposure to digestive enzymes. This will allow for more digestion and absorption of nutrients for normal biomass production. Also, the considerable increase of AD enables the infected and nutrient-deficient larvae to meet their energy and developmental requirements (Shaurub*et al*., 2020) (See Table 2).

Table 2. Mean (± SE) approximate digestibility (AD; %) of *Spodoptera littoralis* infected as fourth instars with the LD_{50} of *Steinernema riobrave*, *Heterorhabditisbacteriophora*, or *Beauveria bassiana*.

Instar	Age of instar (days)	Control	*S. riobrave*	*H.bacteriophora*	*B. bassiana*
Fourth	2[1]	94.12 ± 5.80	92.70 ± 0.68	78.12 ± 2.30*	91.67 ±2.10
	3	88.79 ± 6.60	89.30 ±0.80	87.16 ± 4.80	91.78 ± 3.40
Fifth	1	89.00 ± 4.20	84.34 ± 3.40	88.69 ±4.68	93.73 ± 7.80
	2	82.22 ± 3.40	88.20 ± 3.60	81.66 ±6.70	86.28 ± 4.30
Sixth	1	75.88 ± 3.70	83.17 ±2.00*	75.86 ± 2.00	85.16 ± 5.40*
	2	67.36 ± 2.00	77.66 ±5.40*	68.87 ± 3.00	76.74 ± 3.40*
	3	68.62 ± 6.20	72.77 ± 3.70*	68.00 ± 6.20	80.91 ± 3.60*

[1]Newly moulted 4th instar larvae were first infected for 24 hr before conducting the experiments. *Significant difference between treatment and the respective control (Student's *t*-test: P<0.05) (After Shaurub *et al*., 2020).

With regard to the ECI, infection of the *S. littoralis* 4th instar larvae with *S. riobrave* resulted in increasing ECI of 2-day-old 4th instar larvae and 1-day-old 5th instar larvae but decreased ECI in 3-day-old 4th instar larvae. On the other hand, infection of larvae with *H. bacteriophora* led to increased ECI of 2-day-old 4th instar larvae and 1-day-old 6th instar larvae but decreased ECI of 2- and 3-day-old 6th instar larvae (Shaurub*et al*., 2020). In respect of ECD, its value increased in 1-day-old 5th instar larvae but was decreasedin 1-day-old 6th instar larvae after infection of 4th instar larvae with *S. riobrave*. After infection with *H. bacteriophora*, ECD value of 2-day-old 4th instar larvae and 1-day-old 6th instar larvaeincreased but decreased during the remaining 6th instar duration (Shaurub*et al*., 2020). To explicate the considerable reduction of these food utilization efficiencies of *S. littoralis* late 6th and early 5th instars after infection with *H. bacteriophora*, it can be suggested that most of the ingested or digested food was metabolized for energy production, and it is likely that the major portion of this energy was utilized for defense against the invading pathogens (Shaurub*et al*., 2020).

However, these food utilization efficiencies are reflectedon the larval growth of *S. littoralis*. After infection with *S. riobrave*, GR of 3-day-old 4th instar larvaewas decreased but increased for 5th larval instar. After infection with *H. bacteriophora*, GR of 2-day-old 4th instar larvae and 1-day-old 6th instar larvae increased but decreased of 3-day-old 4th instar larvae and 2- and 3-day-old 6th instar larvae (Shaurub*et al*., 2020).

2. Drastic Impacts of EPNs on Developmental and Reproductive Physiology OfThe Insect Pests:

Death of the insect host is usually reached within 24-72 h post-infection with EPNs (Shapiro-Ilan and Brown, 2013; Shaurub*et al*., 2014; Lacey *et al*., 2015; Leonar*et al*., 2022; Kaliaskar*et al*., 2022). However, several authors (Peschiutta*et al*., 2014; Cardoso *et al*., 2015; Ansari and Hussain, 2020; Shah *et al*., 2021) reported the success of some infected individuals to survive toxic effects of both EPN and its symbiotic bacteria with immune defences. These infected individuals can transform into the next developmental stage but are usually unhealthy because certain biological and physiological processes have been detrimentally affected. In this regard, there has been increasing evidence that some EPNs adversely affect certain metabolic processes in the insect host (Shaurub*et al*., 2020; Ghoneim *et al*., 2022) and some important enzymatic activities (Shaurub*et al*., 2015; Ibrahim *et al*., 2015; Shairra*et al*., 2016; Vidhya *et al*., 2016).

Ghoneim *et al*. (2023b) observed a few EPN-infected 4th instar larvae of *A. ipsilon* pupating at the lower two concentrations of *S. carpocapsae* and *H. bacteriophora*. In this study, also, a similar result was recorded after infection of 5th instar larvae with *S. carpocapsae*. In addition, some studies, on various agricultural insect pests, recorded the capability of some EPN-infected pupae to metamorphoses into adults indicating some resistance of the pupal stage to EPNs (Malan *et al*., 2011; Odendaal *et al*., 2016; du Preez *et al*., 2021a, b; Steyn *et al*., 2021). In a study of Filgueiras and Willett (2021), EPNs can affect the developmental durations and changes in the risk of death of the non-susceptible pupal stage of the onion fly *Delia antique* (Diptera: Anthomyiidae), indicating an insect resistance to infection during the pupal stage. Inactivation of EPN during the pupal stage of an insect and re-establishment of its activity during the adult stage indicate the ability of this EPN to overcome the insect's immune system (Vallet-Geley *et al*., 2008).

The available literature contains little information concerning the effects of EPNs on the biological, physiological and adult performance parameters of mosquitoes (Diptera) until 2022. Early, Welch and Bronskill (1962) found the pupation of some EPNs-infected larvae of the yellow fever mosquito *Aedes aegypti* (Culicidae) with *S. carpocapsae* 1 or 2 weeks longer than the normal congeners (*i.e*., prolongation of larval period), while others failed to

pupate and then died after 3 or 4 weeks. Also, Obiamiwe and Mac Donald (1973) recorded a delay of development of the *Anopheles* (Culicidae) larvae after infection with the nematode *Octomyomermismuspratti*. According to Liu *et al*. (2020b), EPN*Steinernema abbasi* isolate could cause a delay in the next molt and pupation of the Asian tiger mosquito *Aedes albopictus* (Culicidae). Also, Elbrense et al. (2022) recorded significantly prolonged pupal duration of *Cx. pipiens* as an effect of infection with LC_{50} of EPN *R. iyengari* pre-parasites. For more detail, see review of Ghoneim and Bakr (2024).

Prolongation of the pupal duration, or delay of the pupal ecdysis, of mosquito larvae infected with mermithid nematodes owing to a disturbance in their endocrine regulation or due to the insertion of some neurosecretory compounds by the mermithid nematode *Romanomer misiyengari* (Petersen and Willis, 1970). Also, this result may be related to the insufficient nutritional reserves, which are essential for building adult structures during the pupal stage, because EPNs absorb nutrients in the host's body through their body surface (Schmidt and Platzer, 1980; Gordon, 1981). In this regard, the haemolymph protein content of the mosquito *Cx. pipiens* larvae was depleted to one-sixth of the level in normal larvae after infection with the mermithid nematode *Romanomermis culicivorax* (Schmidt and Platzer, 1978). Also, the scarcity of nutritional reserves in mosquitoes may be due to the degeneration of the mid-gut epithelium leading to starvation, as recorded for the mosquito *Aedes aegypti* larvae after infection with *R. culicivorax* (Bailey and Gordon, 1973).

Infection of pupae (the soil dwelling stage) of Tobacco thrips *Frankliniella fusca* (Thysanoptera: Thripidae) with *H. bacteriophora* (Fl1-1), *S. feltiae*, *S. riobrave* or *S. rarum* resulted in reduction of the adult emergence (Gulzar *et al*., 2021). After treatment of pupae of European grapevine moth *Lobesiabotrana* (Lepidoptera: Tortricidae) with high IJ concentrations of four EPN species (*S. feltiae, S. carpocapsae, S. riojaense* and *H. bacteriophora*), adult emergence of the insect was significantly blocked (Vicente-Díez *et al*., 2021). In Egypt, Elbrense*et al*. (2022) treated *Cx. pipiens* 4th instar larvae with LC_{50} of *R. iyengari* pre-parasites and observed partial blockage of adult emergence but no effect on the adult longevity.

Gordon (1981) suggested that EPN-infected adults suffer from being sterilized or biologically castrated. According to Elbrense *et al*. (2022), the treatment of *Cx. pipiens* 4th larval instar with LC_{50} of *R. iyengari* pre-parasites resulted in a considerable reduction of the female fecundity. This reduction of fecundity may result from non-selective use of mosquito energy reserves under stress of EPN infection (Baudoin, 1975). On the contrary, no effect was recorded on the egg-hatching rate of *Cx. pipiens* after infection of 4th instar larvae with LC_{50} of *R. iyengari* pre-parasites (Elbrense*et al*. (2022).

3. Enzymatic Disturbance in Insect Pests Infected with EPNs:

Insect defenses and immune reactions in response to EPN infection have been studied only in a few EPN species-insect species combinations (Lewis and Clarke, 2012; Shapiro-Ilan *et al*., 2018).Some authors (Brown *et al*., 2006; Ffrench-Constant *et al*., 2007; Toubarro*et al*., 2009) reported that EPNs in the families of SteinernematidaeandHeterorhabditidae are lethal endoparasites of insects because they can secrete active substances, including toxins, proteases, and so on, contributing to the lethal effect on infected host insects. The lethal activity of EPNs is often closely related to the activity disturbance of some important enzymes in the host insects (Grewal *et al*., 2005; Ahmed *et al*., 2014; Ibrahim *et al*., 2018, 2019). Many EPNs secrete chemicals that facilitate penetration and migration through host tissues, feeding, and avoidance of host immune responses. These chemicals include digestive enzymes and toxins (Lee and Atkinson, 1976). Beside these secretions, the EPN-symbiotic bacteria also secrete certain toxins for suppressing the immune responses of the host insect leading to the host death (Koppenhöfer, 2007; Richards and Blair, 2010). For instance, *Xenorhabdus nematophila*, the symbiont bacterium of *S. carpocapsae*, secretes several enzymes, including

hemolysins, lipases, and proteases, which are thought to contribute to the virulence or nutrient acquisition for the bacterium and its nematode host *in vivo* (Van Damme *et al*., 2016; Askitosari*et al*., 2021; El Aalaoui*et al*., 2022). Disturbances in the enzymatic activity during the progress of pathogen play an important role for understanding the interaction between the pathogen and host as a part of a survival strategy (Ibrahim *et al*., 2015).

3.1. Disturbed Activities of the MajorDigestive Enzymes in Insects:

In insects, digestive enzymes are primarily generated and secreted by the midgut epithelium of the alimentary duct (Chapman, 1998). Two digestive enzymes, amylase and protease, were also found in the salivary gland complex (Li *et al*., 2017; Holtof*et al*., 2019). The digestive enzymes lipase, amylase, and protease, which metabolize sugars, lipids, cellulose, and proteins in the mid-gut of an insect, are extremely important for the energy production and the food metabolism in insects (Gökkuş*et al*., 2016; Bonelli *et al*., 2020). It is important to provide an insight into the disruptive effects of EPNs on activities of the main digestive enzymes of various categories.

3.1.1. Activity Disturbance of Carbohydrate Hydrolyzing Enzymes:

In insect physiology, it is well-known that themetabolism of carbohydrates is regulated mainly by carbohydrate hydrolyzing enzymes. Glycosidases catalyse cleavage of internal bonds in polysaccharides and hydrolyse oligosaccharides as well as disaccharides (Zibaee*et al*., 2008b). In the present review, we shed some light only on three digestive enzymes, amaylase, trehalase and invertase.

Disturbed AmaylaseActivity by EPNs:

Amylases are necessary enzymes to hydrolyze carbohydrates present in the insect larvae. They catalyze the hydrolysis of α-D-(1,4)-glucan linkages in glycogen and other related carbohydrates (Franco *et al*., 2000). Amylases are secreted by salivary glands and mid-gut of larvae (Ribeiro *et al*., 2000). Depending on the available literature, amylase activity increased or decreased, depending on the insect species, the EPN species, applied concentration, the EPN-symbiotic bacteria and the time of infection. For example, Zółtowska (2004) reported an increase of the enzyme activity in 7th instar larvae of the greater wax moth *Galleria mellonella* (Lepidoptera: Pyralidae) at 48 h post-infection with 20 IJ/insect of the EPN *Heterorhabditiszealandica*. Two years later, Zółtowska and Łopieńska (2006) recorded a significant reduction in the enzyme activity after infection of last instar larvae of *G. mellonella* with EPNs *Steinernemaaffinis* and *S. feltiae*, at different exposure periods except a significant increase at 12, 18 and 24 h post-infection with *S. feltiae*. Also, amylase activity was decreased in *S. littoralis* larvae after infection with *H. bacteriophora* but increased after infection with *S. riobrave* or *S. feltiae* (Ahmed *et al*., 2014). After infection of the 4th larval instar larvae of *A. ipsilon* with *H. zealandica* or *S. abbasi*, amylase activity was reduced (Ibrahim *et al*., 2015).

Some years later, Shaurub*et al*. (2020) incubated the newly moulted 4th instar larvae of *S. littoralis* with LD_{50} of EPNs *S. riobrave* and *H. bacteriophora* for 24 h and determinedincreasing amylase activity. Also, four EPNs, *H. bacteriophora*, *S. carpocapsae*, *Steinernema scapterisci*, *S. glaseri* were assessed against the last instar larvae of *G. mellonella* by Khater *et al*. (2020) in Egypt. Their results demonstrated that infection with the concentration 20 IJs of *H. bacteriophora* or *S. carpocapsae* resulted in a significant reduction of the amylase activity, but both *S. scapterisi* and *S. glaseri* caused a slight increase, 6 h post-infection. At concentration 50 IJs, a significant elevation in the enzyme activity was recorded at 6 h post-infection. Meanwhile, *H. bacteriophora* caused a significant reduction in enzyme activity at 12 and 48 h post-infection. After infection of the larvae of fruit flies *Bactrocerazonata* and *C. capitata* with the EPN *S. carpocapsae*, Elhadidy*et al*. (2021) recorded a significant decrease but a slight increase of the enzyme activity in these two fly species, respectively. In a recent study, Fathy and Abd El-Rahman (2023) infected the 5th

instar nymphs and adults of the African migratory locust *Locusta migratoriamigratorioides* (Orthoptera: Acrididae) with the LC_{50} of *Steinernema* spp. and *H. bacteriophora* and estimated reduced amylase activity. Due to the toxic effects of the EPNs, *Stienernema* spp., the *H. bacteriophora*, and their associated bacteria, considerably reduced amylase activity was determined (Muhammad *et al*., 2022).

Disturbed TrehalaseActivity by EPNs:

Because trehalaseplays an important role in energy supply, it is one of the most important carbohydrases in insects, hydrolyzing trehalose (the main sugar in insect haemolymph) into two glucose molecules (Shukla *etal*., 2015). As reported in the available literature, results of several studies revealed the inhibition and reduction of trehalase activity in several insects as a result to the infection with different EPNs. For instance, Dmitryjuk*et al*. (2001) recorded a slight decrease of enzyme activity in the 3rd instar larvae of *G. mellonella* after infection with the infective juvenile (IJs) of *S. affinis*. Also, Zółtowska and Łopieńska (2006) determined a significant decrease of the enzyme activity in 7th instar larvae of *G. mellonella* at 6 and 12 h post-infection with *S. affinis* or *S. feltiae*. After infection of the 4th larval instar larvae of *A. ipsilon* with *H. zealandica* and *S. abbasi*, trehalase activity was reduced (Ibrahim *et al*., 2015).

In addition, infection of the last instar larvae of *G. mellonella* with concentration 100 IJs of *H. bacteriophora* resulted in an inhibition of trehalase activity at 6, 24 and 48 h post-infection (Khater *et al*., 2020). In Egypt, Elhadidy*et al*. (2021) infected the larvae of the fruit flies *B. zonata* and *C. capitata* with *S. carpocapsae* and recorded remarkably decreased enzyme activity in *B. zonata* but a slight reduction in *C. capitata*. In Egypt, also, Fathy and Abd El-Rahman (2023) infected the 5th instar nymphs and adults of *L. migratoria migratorioides* with the LC_{50} of *Steinernema* spp. and *H. bacteriophora* and estimated decreasing trehalase activity.

Energy demands are stepped up in the insect host in initial stage of EPN infection, when the physiology of the host is changed to combat the disease as a natural response. Therefore, the decrease ofenzyme activity in the EPN-infected larvae can be attributed to decreased metabolic capabilities of these larvae. This is, also, due to decreased hydrolysis of trehalase to release glucose molecules under drastic stress conditions and high energy requirement (Hasegawa and Yamashita, 1970; Ibrahim *et al*., 2015). In addition, this reduction may be due to the toxic effects of the EPNs and/or their symbiotic bacteria (Muhammad *et al*., 2022).

Trehalase activity in some insects increased after infection with certain EPNs. For example, Zółtowska (2004) reported an increase of the enzyme activity in 7th instar larvae of *G. mellonella* at 18 and 24 h post-infection with 20 IJ/insect of *H. zealandica*. Also, the enzyme activity increased in the *S. littoralis* larvae after infection with *H. bacteriophora*, *S. riobrave* or *S. feltiae*. The highest increase was determined in case of infection with *S. riobrave* (Ahmed et al., 2014). Depending on a study conducted by Shaurub*et al*. (2020) in Egypt, the newly moulted 4th instar larvae of *S. littoralis* were infected with LD_{50} of *S. riobrave* or *H. bacteriophora* for 24 hr. As a response to the EPN infection, trehalase activity was promoted. However, considerable activity increases of carbohydrate-hydrolyzing enzymes, particularly trehalase, may be expected to increase the availability of glucose, both for the defense mechanisms of the insect host and for development of the invading pathogen (Shaurub*et al*., 2020).

Disturbed InveratseActivity by EPNs:

From the physiological point of view, invertase cleave sucrose into the monosaccharides, glucose, and fructose. This enzyme is secreted in the gut of insect larvae (Heil *et al*., 2005). Some authors reported a reduction of invertase activity in some insects by certain EPN species, such as Ibrahim *et al*. (2015) who recorded decreasing activity after

infection of the 4th larval instar larvae of *A. ipsilon* with the EPNs *H. zealandica* or *S. abbasi*. Also, the enzyme activity was remarkably inhibited in the larvae of *B. zonata* and *C. capitata* after infection with *S. carpocapsae* (Elhadidy*et al*., 2021). Fathy and Abd El-Rahman (2023) infected the 5th instar nymphs and adults of *L. migratoriamigratorioides* with the LC_{50} of *Steinernema* spp. and *H. bacteriophora* and estimated decreasing activity of invertase. The inhibition of invertase activity in these insects may be due to the EPNs themselves or/ and their associated symbiotic bacteria (Muhammad *et al*., 2022).

In contrast, invertase activity increased in *S. littoralis* larvae after infection with *H. bacteriophora*, *S. riobrave* or *S. feltiae*. The highest increase in activity was observed in the case of infection with *S. riobrave* (Ahmed *et al*., 2014). According to Shaurub*et al*. (2020), incubation of the newly moulted 4th instar larvae of *S. littoralis* with the LD_{50} of EPNs *S. riobrave* and *H. bacteriophora* for 24 h resulted inincreasing invertase activity. Furthermore, increase and decrease of invertase activity had been reported in the same insect after infection with the same EPN species, depending on the time interval post-infection. For instance, Khater *et al*. (2020) assessed the efficiency of four EPNs, *H. bacteriophora*, *S. carpocapsae*, *S. scapterisci*, *S. glaseri* against the last instar larvae of *G. mellonella*. Depending on their results, the infection with concentration 20 IJs of all EPNs resulted in a significant decrease of the invertase activity at 6 and 12 h post-infection, but a significant increase at 24 h.

3.1.2. Activity Disturbance of Protein Hydrolyzing Enzymes:

Peptidases (peptide hydrolases) include proteinases (endopeptidases) and (exopeptidases) (Terra and Ferriera, 2005). In insects, proteinases, also known as proteases or proteolytic enzymes, are involved in the digestive processes, proenzyme activation, liberation of physiologically active peptides, complement activation and inflammation processes amongst others (Macedo and Freire, 2011). These enzymes catalyze the hydrolysis of peptide bonds in proteins and polypeptides (Zibaee, 2012). Serine and cysteine proteinases are the major proteinase classes in the digestive systems of phytophagous insects (Haq *et al*., 2004).

As previously described, IJs of many EPN species secrete chemicals to facilitate their penetration through the host tissues. These chemicals include digestive enzymes and toxins. Therefore, proteases are suggested as essential enzymes for the pathogenicity of the many EPNs. Haemolymph of larvae of many insects contains inhibitor (s) that inhibits proteases of both the invading IJs and their symbiotic bacteria. The inhibitor is produced during the second period of infection when the larval defense system has already been overcome and infection is established (Kucera and Mracek, 1989). For instance, when IJs of EPN *S. glaseri* were treated with protease inhibitors and injected into *G. mellonella* gut, the mortality% of larvae was reduced, and the nematode penetration of the larval gut was reduced (Abu Hatab *et al*., 1995). Digestive enzyme inhibitors have been reported to be important in the control of insect pests (Franco *et al*., 2000; Mehrabadi *et al*., 2012).

Besides digestion, trypsin-like enzymes contribute in a wide range of other physiological processes in insects, such as molting (Wei *et al*., 2007), tissue remodeling (Liu *et al*., 2009), innate immunity (Kanost*et al*., 2004), diapause (Chen *et al*., 2005), fertilization (Friedlander *et al*., 2001), and activation of enzyme precursors of trypsin, chymotrypsin (Parde *et al*., 2012), chitinase (Royer *et al*., 2002), and phenoloxidase (Yu and Kanost, 2004). In addition, trypsin can affect biology of the pathogenic organisms (Nakazawa *et al*., 2004; Darpel *et al*., 2011) and may have a role in preventing infection by parasites (Jochim *et al*., 2008; Sant'Anna *et al*., 2009).

The current literature contains very few studies investigating the inhibition of protease activity in some insects after infection with certain EPN species (Wang *et al*., 2012; Ibrahim, *et al*., 2018). The protease activity in haemolymph of the infected 4th instar larvae of *A. ipsilon*decreased after 16 h of infection with *H. zealandica* or *S. abbasi* (Ibrahim *et al*., 2015).

The determined decrease in protease activity could be due to the symbiotic bacteria beginning to digest the proteins of the insect body 16 h post-infection (Ibrahim *et al*., 2015). Fathy and Abd El-Rahman (2023) infected the 5th instars and adults of *L. migratoriamigratorioides* with LC_{50} of *Steinernema* species and *H. bacteriophora* and estimated decreasing activity of protease.

3.1.3. Activity Disturbance of Lipid Hydrolyzing Enzymes:

Lipases catalyze the hydrolysis of fatty acid ester bonds (Grillo *et al*., 2007). They are able to hydrolyze a variety of esters in organic solvent systems (Zibaee*et al*., 2008a). Also, hydrolysis of triacylglycerol into its free fatty acids and glycerol backbone is one of the many reactions that lipaseis involved enzyme (Yao *et al*., 2021).

To the best of our knowledge, scarce results were available in the current literature about the impacts of EPNs on the lipid hydrolyzing enzymes in insects. The only available study was conducted in Egypt by Fathy and Abd El-Rahman (2023). They infected the 5th instar nymphs and adults of *L. migratoriamigratorioides* with the LC_{50} of *Steinernema* spp. and *H. bacteriophora* and estimated increasing lipase activity. This result can be understood in view of the activity of EPN-symbiotic bacteria *X. nematophila* or *P. luminescens* which secrete various enzymes, such as hemolysis, lipases, and proteases, that contribute to pathogenicity or nutrient acquisition for the bacterium and its nematode host, lipase activity was dramatically boosted (Richards and Blair, 2010).

3.1.4. Activity Disturbance of Some Digestion-Related Enzymes:

As reported by several authors (Merzendorfer and Zimoch, **2003**; Subbanna *et al*., 2018; Henriques *et al*., 2020), chitin is mostly produced by fungi, arthropods, and nematodes and makes up a significant portion of the insect cuticle (a complicated layer in the body wall). It supports the cuticles in the body wall and trachea, the peritrophic matrices lining the gut epithelium, and insect development and morphogenesis in insects. Chitinase protein secreted by the EPN-symbiotic bacteria, *Xenorhabdus*and *Photorhabdus*spp, plays a key role in the virulence of these bacteria by both degrading cuticle of the insect host and accelerating the binding process of toxins to the target sites (Liu *et al*., 2020a; Mahmood *et al*., 2020). Results of Gümüssoy*et al*. (2022) on the codling moth *Cydia pomonella* (Lepidoptera: Tortricidae) suggested that toxic metabolites, including chitinase protein, are present in the cell-free supernatant of symbiotic bacteria and are responsible for mortality. Fathy and Abd El-Rahman (2023) infected the 5th instar nymphs and adults of *L. migratoriamigratorioides* with LC_{50} of EPN *Steinernema* spp. and *H. bacteriophora* and estimated increasing activity of chitinase. Due to the presence of EPN-symbiotic bacteria, *X. nematophila* or *P. luminescens*, which create chitinase for their growth rate, the amount of chitinase was considerably increased (Chen *et al*., 1996).

3.2. Disturbed Activities of the Major Detoxifying Enzymesin Insects Infected with EPNs:

In insects, detoxification enzymes have many functions for repairing physiological processes, detoxifying pathogenic products, and metabolizing the biologically active compounds (Visetson and Milne, 2001; Zhu-Salzman and Zeng, 2015). Also, they play a crucial role for decomposing toxic substances into non-toxic constituents, decreasing the toxicity of xenobiotics in order to maintain the normal physiological and biochemical criteria in the body (Mukanganyama*et al*., 2003; Li and Liu, 2007) as well as they act as protectants against different oxidative stresses (Zibaee*et al*., 2011).

In insects, detoxification can be achieved by different families of enzymes including esterases (ESTs), phosphatases, transaminases, glutathione S-transferase (GSTs), glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SODs), catalases (CATs), monooxygenases (MOs), acetylcholinesterase (AchE), multi-function oxidases (MFOs), peroxidases (PODs), as well as tyrosinase (TYR) and carboxylesterase (CarE)(Li

et al., 2007; Zibaee*et al*., 2011). However, Li *et al*. (2022) reported SODs, PODs, and CATs as antioxidant enzymes and CarE, GST and AchE as detoxifying enzymes, since insects are known to use antioxidants and detoxifying enzymes in their immune systems as defense reactions against pathogen threats (Dubovskiy*et al*., 2012). On the other hand, antioxidant enzymes possess the function of scavenging excessive reactive oxygen species (ROS), degrading hydrogen peroxide (H_2O_2), and preventing free-radical-associated damage (Dubovskiy*et al*., 2008; Zhou *et al*., 2019). In general, insects activate several defense mechanisms, *viz*., Phenoloxidase, hemocytes, detoxification and antioxidant enzymes (Lalitha *et al*., 2018). Therefore, fluctuation in activities of these enzymes may have an impact on the insect adaptability to the surrounding environment (Serebrov *et al*., 2001, 2006; Li *et al*., 2016).

3.2.1. Disturbed Activities of Phosphatases in Insects:

As clearly reported by some authors (Srinivas *et al*., 2004; Zheng *et al*., 2007), phosphatases have been included in the category of detoxifying enzymes. As a lysosomal enzyme, acid phosphatase (ACP) may have a role in autophagy and cell turnover as well as defense (Xia *et al*., 2000). ACP and alkaline phosphatase (ALP) are hydrolytic enzymes, and they are responsible for removing phosphate groups from many types of molecules, including nucleotides, proteins, and alkaloids in alkaline and acidic conditions, respectively in a process called 'dephosphorylation' (Zibaee*et al*., 2011). These two phosphatases not only hydrolyze phosphate groups from the ingested toxic molecules and naturally occurring ones, but also their activities may refer to the efficiency of digestion and transportation within insect body (Nation, 2008; Zibaee*et al*., 2011). Appearance of ALP in the plasma membrane, its activity is affected due to cell membrane damage, so ALP is also considered as a biomarker for cellular stress (Lalitha *et al*., 2018).

***Disturbed Activity of ACP in Insect*s:**

According to the current literature, there are many reported results of increasing ACP activity in larvae of various insects after infection with different EPN species, such as larvae of *C. capitata* after infection with *S. riobrave* and *H. bacteriophora* (Soliman, 2002); larvae of *S. littoralis* after infection with *S. riobrave* and *H. bacteriophora* (Ahmed *et al*., 2014); *A. ipsilon* 6th instar larvae at 6 hr post- infection with *S. glaseri* or *H. bacteriophora* (Hassan *et al*., 2016); the 5th nymphs of *S. gregaria* after infection with 1000 IJs of *H. bacteriophora* (Gaber *et al*., 2018); the 3rd instar larvae of *S. littoralis* after infection with *H. bacteriophora* or *S. carpocapsae* (Gomaa *et al*., 2020); and the 4th instar larvae of *S. littoralis* after infection with LD_{50} values of *S. riobrave* or *H. bacteriophora* for 24 h (Shaurub*et al*., 2020). Ghoneim*et al*.(2023a) determined significantly increased ACP activity in haemolymph of 6 h-old last instar larvae of *A. ipsilon* after infection of the penultimate instar larvae with *S. carpocapsae* or *H. bacteriophora*. Moreover, *H. bacteriophora* exhibited a higher enhancing potency on the enzyme activity than *S. carpocapsae*, at this time (See Table 3). In addition, increased ACP activity had been reported in haemolymph of some insects after infection with some entomopathogens (Xia *et al*., 2001; Mirhaghparast*et al*., 2013; Vidhya *et al.*, 2016).

The increasing ACP activity in larvae of these insects after infection with certain EPNs may indicate a physiological adaptability to combat the oxidative stressor may be related to an inhibition of lipid peroxidation process and physiological response mechanism against the EPN toxic secretions. Also, the increasing activity of ACP may be attributed to its role in the transportation of lipids, such as monoacylglyceroles, through low density lipoproteins to supply the energy demands of the treated larvae (Khorshidi *et al*., 2019). In addition, the increaseof ACP activity in larvaemay be due tothephagocytosis of certain hemocytes to the invading EPNs, since phagocytosis is known to stimulate the production of lysosomal enzymes, and ACP acts as a lysosome marker (Xia *et al*., 2000; Hassan *et al*., 2016). In other words, the increase of ACP activity in haemolymph may be an attempt by the

infected larvae to defend against the invading pathogens, where lysozymes are a component of humoral immunity (Mohamed *et al*., 2016; Satyavathi *et al*., 2018; Dorrah *et al*., 2019).

Table 3. Acid phosphatase activity inhaemolymph (U/L) of last (6^{th}) instar larvae of *A. ipsilon* as influenced by infection of the newly moulted 5^{th} instar larvae with LC_{50} values of the tested Entomopathogenic nematodes.

Nematode species		Time interval		
		6 hr	24 hr	48 hr
S. carpocapsae	mean±SD	98.56±2.17 b	54.45±1.02 c	41.26±1.31 c
	Change (%)	+44.62	-30.38	-49.57
H. bacteriophora	mean±SD	115.18±1.93 c	70.72±1.21 b	57.29±1.10 b
	Change (%)	+69.01	-9.59	-29.98
Control	mean±SD	68.15±2.10	78.22±1.95	81.82±2.53

B, c: see footnote of table 1.(After Ghoneim *et al*., 2023).

In contrast, ACP activity was remarkably decreased in haemolymph of 24 and 48 hr-old last instar larvae of *A. ipsilon*, after infection of the penultimate instar larvae with *S. carpocapsae* or *H. bacteriophora* (Ghoneim *et al*.,2023a). To some extent, similar results of decreasedACP in some insect larvae after infection with some EPN species had been reported, such as the late 3^{rd} instar larvae of *C. capitata* after infection with *H. bacteriophora* AS1, *H. bacteriophora* HP88, *S. carpocapsae* ALL, and *S. riobrave* ML29 (Shaurub*et al*., 2015) and 5^{th} nymphs of *S. gregaria* after infection with 2000 IJs (high concentration) of *H. bacteriophora* (Gaber *et al*., 2018). For some detail, see studies of Żółtowska*et al*. (2006), Wu *et al*. (2013) and Ahmed *et al*. (2014).

However, the decrease of ACP activity can be due to the inability of the cell to undergo enzymatically controlled reactions under EPN infection (Soliman, 2002). In addition, decreasing ACP activity may be due to the reduced phosphorus liberation for energy metabolism and decreased rate of metabolism, as well as decreased rate of transport of metabolites (Senthil Nathan *et al*., 2005). Also, the decline of ACP level in larvae, as a response to infection with the present EPNs, may be due to strong inhibition of ecdysone which is followed by subsequent decrease in number of lysosomes and in turn declined level of ACP (Hassan, 2002).

***Disturbed Activity of ALP in Insects*:**

Based on the available literature, there are many reported results of increasing ALP activity in several insects as response to the infection with certain EPNs. For instance, Soliman (2002) recorded an increase of ALP activity in the last instar larvae of *C. capitata* after infection with *S. riobrave* or *H. bacteriophora*. In Egypt, Ahmed *et al*. (2014) reported an increasing activity of ALP in *S. littoralis* larvae as response to the infection with *S. riobrave* or *H. bacteriophora*. Also, ALP activity increased in the 3^{rd} instar larvae of *S. littoralis* after infection with two EPN isolates (*H. bacteriophora* and *S. carpocapsae*) and the entomopathogenic fungus *Beauveria bassiana*, separately on in combination (Gomaa *et al*., 2020). In addition, increasing activity of ALP was recorded in 4^{th} instar larvae of *S. littoralis* after incubation with the LD_{50} values of *S. riobrave* and *H. bacteriophora* for 24 h (Shaurub*et al*., 2020). Recently, Ghoneim*et al*. (2023a) obtained results consistent with those reported results, since ALP activity increased in the haemolymph of *A. ipsilon* at 6 hr of last instar larvae after infection of penultimate instar larvae with *S. carpocapsae* or *H .bacteriophora*.

On the contrary, ALP activity in larvae of some insects was reduced after infection with certain EPNs, such as a slight decrease of ALP activity in *S. littoralis* larvae after infection with *S. feltiae* (Ahmed *et al*., 2014); significantly declined ALP level in the late 3^{rd}instar larvae of *C. capitata* after infection with four EPNs *H. bacteriophora* AS1, *H. bacteriophora*

HP88, *S. carpocapsae* ALL and *S. riobrave* ML29 (Shaurub*et al*., 2015); and decreasing activity of ALP in the 5th instar nymphs of *S. gregaria* at 1000 and 2000 IJs of *H. bacteriophora* (Gaber *et al*., 2018). Also, significantly declined ALP activity was recorded in some insects infected with other EPNs (Żółtowska*et al*., 2006; Wu *et al*., 2013). In accordance with these reported results, Ghoneim*et al*. (2023a) found a considerable reduction of ALPactivity in haemolymph of 24 h- and 48 h-old last instar larvae of *A. ipsilon*after infection of penultimate instar larvae with *S. carpocapsae* or *H. bacteriophora*. Depending on the reduction of ALP activity at 48 h, *S. carpocapsae* exhibited stronger reducing potency than *H. bacteriophora*.

3.2.2. Disturbed Activities of Transaminasesin Insects:

Glutamic oxaloacetic transaminase (GOT, or Alanine aminotransferase, ALT) and Glutamic pyruvic transaminase (GPT, oraspartate aminotransferase, AST) are the key enzymes of transamination within the intermediary metabolism of insects to make amino acids available for essential biochemical requirements (Plant and Morris, 1972). Some authors (Içen*et al*., 2005; Etebari*et al*., 2005) reported that these transaminases constitute a strategic link between carbohydrate and lipid metabolism. Activities of these enzymes are known to be disturbed under various physiological and pathological conditions. In other words, disturbance of these enzymes in insects denotes biochemical impairment and lesions of tissues and cellular function because they are involved in the detoxification processes and metabolism (Enan and Berberian, 1986).

There are many reported results of decreased activities of transaminases in some insects after infection with certain EPNs. For instance, GOT and GPT activities were decreased in *C. capitata* last instar larvae after infection with *S. riobrave* and *Heterorhabditis* sp. (Soliman, 2002). Activities of both enzymes were significantly decreased in the late 3rd instar larvae of *C. capitata* after infection with *H. bacteriophora* AS1 and *S. carpocapsae* ALL (Shaurub*et al*., 2015). The activities of these enzymes were remarkably decreased in the 4th instar larvae of *S. littoralis* at 48 h post-infection with *H. bacteriophora* and *S. riobrave* (Ahmed *et al*., 2014). Also, their activities had been decreased in the 3rd instar larvae of *S. littoralis* after infection with EPNs *H. bacteriophora* and *S. carpocapsae* and the fungus *B. bassiana*, separately on in combination (Gomaa *et al*., 2020). The newly moulted 4th instar larvae of *S. littoralis* were infected with LD_{50} values of *S. riobrave* and *H. bacteriophora* for 24 h, leading to reduction in activities of these transaminases (Shaurub*et al*., 2020). In a recent study of Ghoneim *et al*. (2023a), the disturbance of transaminase activities depended on the time interval post-infection, since GOT activity significantly increased in the haemolymph of *A. ipsilon* last instar larvae at 6 h post-infection with *S. carpocapsae* or *H. bacteriophora*. At 24 h, GOT activity considerably increased by *H. bacteriophora* while decreased by *S. carpocapsae*. At 48 h time interval, GOT activity was remarkably decreased by both EPNs. With regard to GPT, its activity was predominantly declined after infection with *S. carpocapsae* or *H. bacteriophora*, at all-time intervals, with few exceptions.

To explain the reduction of GOT and GPT activities in the insect larvae after infection with some EPNs, some suggestions can be accepted. The decreasing activities of these enzymes may be attributed to the significant decline in the free amino acids content (Kaur *et al*., 1985), the quantum of which directly influences the activity of transaminases at the time of protein synthesis (Soliman, 2002). Also, it may be due to a disruption of the link between carbohydrates and protein metabolism (Azmi *et al*., 1998). Reduction in transaminase activities has been indicated to lead to the required reduction in the host protein synthesis, since these are generalized enzymes involved in dephosphorylation and energy transfer (Shaurub*et al*., 2020). Also, reduction of GPT activity may be due to the interference of the EPNs with the hormonal regulation of protein synthesis and neurosecretory hormones involved in the regulation of transaminase levels (Abulyazid*et al*., 2005). In addition, this

reduction of GPT activity may bedue to the effects of EPNs on the synthesis or functional levels of this enzyme directly or indirectly by altering the cytomorphology of the cells (Nath, 2000).

3.2.3. Disturbed Activity of Acetylcholinesterase in Insects:

Acetylcholinesterase (AchE, EC 3.1.1.7) is a key enzyme for catalyzing the hydrolysis of acetylcholine (Ach), a neurotransmitter, in the nervous system (Wang *et al*., 2004; Zibaee, 2011). AchE is primarily responsible for the termination of cholinergic neurotransmission at synapses in both insects and humans (Carlier *et al*., 2008). Inhibition of AchE results in an excessive accumulation of Ach in the synapses which in turn leaves the Ach receptors permanently open, leading to hyperactivity and consequently paralysis and death (Soreq and Seidman, 2001; Fournier, 2005). AchE activity is one of the main resistance mechanisms in various insect species against the chemical insecticides, like organophosphrous compounds, since it degrades (through its hydrolytic activity) the neurotransmitter Ach, producing choline and an acetate group (Kozaki*et al*., 2001; Li and Han, 2002; Yu, 2006).

Many studies have focused on the activity of AchE of insects for investigating insecticide toxicology, but few studies reported the effects of EPNs on AchE activity in insect hosts (Shairra*et al*., 2016b). In this context, the AchE activity in some insects elevated after infection with certain EPNs, as reported by Soreq and Seidman (2001). Also, some investigators (Wu *et al*., 2013; Han-dong *et al*., 2013) recorded significantly increased AchE activity in *G. mellonella* larvae after infecting with EPN *H. beicherriana*..

In Egypt, Ibrahim *et al*. (2015) determined a significant increase of AchE activity in the 4th larval instar larvae of *A. ipsilon* during the first 8 hs of *H. zealandica* infection. In Egypt, also, Shairra*et al*. (2016b) reported that the activity of AchE was significantly enhanced in a dose-dependent manner in *A. ipsilon* larvae after infection with EPN *S. carpocapsae* or *S. scapterisci*. In China, Li *et al*. (2022) investigated the impact of EPNs and entomopathogenic bacteria, separately and in combination, on theAchE activity in the dark black chafer *Holotrichia parallela* (Coleoptera: Scarabaeidae). Based on their results, the enzyme activity was almost enhanced in larvae during the early period (24 h) after infection with *H. beicherriana*, *Bacillus thuringiensis* (*Bt*), or EPN+*Bt* combination. Moreover, the AchE activity after EPN+*Bt* treatment was higher than EPN or *Bt* infection alone.

Inhibition of the AchE activity was determined in 4th larval instar larvae of *A. ipsilon* after infection within*S. abbasi* (Ibrahim *et al*., 2015). The enzyme activity in insects depends on the EPN concentration, since it was enhanced in the mealworm beetle *Tenebrio molitor* (Coleoptera: Tenebrionidae) larvae after infection with lower concentrations of EPN *H. beicherriana*, but was inhibited at higher concentrations (Li *et al*., 2016). Enzyme activity was time post-infection dependent, since Elhadidy*et al*. (2021) recorded a significant increase of activity in the larvae of both fruit flies *B. zonata* and *C. capitata* 24 h post-infection with *S. carpocapsae* that decreased later on.

Increased activity of AchE may be the overreactive stress response to the EPNs infection. This overreaction often leads to death of the host insects (Ibrahim *et al*., 2015; Shairra*et al*., 2016b). Significant increase of AchE was determined in insect larvae 24 h post-infection with EPNs, which correspond to early infection and development of these nematodes and the mass production of the symbiotic bacteria, respectively (Wu *et al*., 2013). According to Li *et al*. (2016), the increase in AchE activity may be correlated with secretions produced by the EPN/symbiotic bacteria complex and may be correlated with the virulence of the EPNs against host insects, although the mechanism of destruction is unknown!

3.2.4. Disturbed Activity of Carboxylesterasein Insects:

Carboxylesterase (CarE) is known as the primary metabolic and hydrolyzing enzyme that hydrolyzes various compounds, including thioester, aliesterase, sulfate, and amides, thus reducing the toxicity of exogenous xenobiotics (Oakeshott *et al*., 2005; Montella *et al*., 2012;

Hatfield *et al*., 2016) or degrading the toxic substances (Zhang *et al*., 2011). In other words, CarE is a crucial detoxifying enzyme playing an important role in insecticide resistance and has been associated with resistance to several insecticide classes in many insects (Ranson *et al*., 2002). Due to its role in insecticide metabolism, determination of CarE activity is used as a biochemical indicator of insecticide resistance in many insects (de Carvalho *et al*., 2006).

In addition to its role in insecticide resistance, the current literature contains some studies investigating the disturbance of CarE activity in several insect pests by the infection with EPNs. For example, activity of CarE was significantly enhanced in a dose-dependent manner in *G. mellonella* larvae after infection with EPN *H. beicherriana* (Wu *et al*., 2013). The CarE activity increased in 4th larval instar larvae of *A. ipsilon* with the increase of time exposure to *S. abbasi* (Ibrahim *et al*., 2015). Based on a study conducted by Li *et al*. (2022), activity of CarEin *H. parallela* larvae was almost enhanced during the early period (24 h) post-infection with EPN *H. beicherriana*, *B. thuringiensis* (*Bt*), or EPN+*Bt* combination. Moreover, the enzyme activity of EPN+*Bt* treatment was higher than EPN or *Bt* infection alone. Also, the CarE activity in insects depends on the EPN concentration, since it was enhanced in *T. molitor* larvae after infection with lower concentrations of EPN *H. beicherriana*, but was inhibited at higher concentrations (Li *et al*., 2016).

According to Wu *et al*. (2013), the significantly enhanced activity of CarE may be the overreactive stress response to the EPNs infection and the overreaction can lead to the death of host insects because many lipids would be disintegrated, which would damage organs and tissues. It seems that the host insects overreacted to the EPNs infection by enhancing the CarE activity first, indicating that many lipids would be disintegrated, which would damage organs and tissues, and lead to the death of insect host. Then, the EPNs-infection response would consume the CarE resulting in decreased CarE activity. Ibrahim *et al*. (2015) explained the increase of CarE activity in larvae as inability to overcome the toxic protein released by the *S. abbasi*-symbiotic bacteria *Xenorhabdus* in the larval haemocoel. For more interpretation, Li *et al*. (2016) proposed that the insecticidal active substances, secreted by the symbiotic bacteria of EPNs during reproduction, can act as xenobiotic toxic substances and induce defensive enzymes, including CarE. Later, the EPNs-infection response can consume the CarE, resulting in decreased CarE activity. This is in accordance with Muñoz *et al*. (2006) who reported that a heavy parasitic burden with a long-established infestation would result in a generalized host weakness, inducing the immune depression and insecticide resistance in invertebrates. On the other hand, the decreases in CarE activity in the larvae infected with *H. zealandica* indicated that the insect immunity system is distributed so it cannot resist the toxic substances released by the symbiotic bacteria *Photorhabdus* in the larvae haemocoel (Ibrahim *et al*., 2015).

3.2.5. Disturbed Activities of Esterases in Insects:

Esterases (ESTs) constitute a large class of enzymes, most of which are important in metabolism because they can break ester bond through hydrolysis (Sivakumarm and Maya, 1991; Hassan and Mohamed, 2008). Also, some ESTs play a critical role in the detoxification of synthetic chemicals (Shen and Dowd, 1991). Non-specific ESTs perform important functions in the degradation of toxins of different origins (Ibrahim *et al*., 2019). Some of these enzymes show the strongest reaction to environmental stimulation (Hemming and Lindroth, 2000). The disintegration inactive poisonous particles with GSTs and ESTs through infections have an opener function in saving insects from pathogens (Dubovskiy*et al*., 2012).

As clearly shown by the available literature, few studies concerned with the impacts of EPNs on the activities of ESTs in insects. For instance, Shairra and Awad (2011) evaluated the effect of EPN *H. bacteriophora* infection on the ESTs activities in nymphs of *S. gregaria*. Depending on their results, α-esterase activity significantly increased by the increasing time of infection, but β-esterase activity severely declined with increasing time post-infection.

Gaber *et al*. (2018) investigated the disruptive effect of the same EPN on the same enzymes in 5th nymphs of the same locust. According to their results, α-esterase activity significantly increased, in a dose-dependent course, but activity of β-estaerase increased at the low concentration and dramatically decreased at high concentration. The 5th instar nymphs of another locust, *L. migratoria*, were infected with EPN *S. carpocapsae* by Abd-El Wahed and Elhadidy (2018). As a result, α-esterase activity significantly decreased at 48 h post-infection but not 24 h, while β-esterase activity significantly increased at 24 h post-infection.

Larvae of *G. mellonella* were infected with LC_{50} concentrations of EPN (*H. zealandica*) and fungus (*B. bassiana*), both separately and in a combination, by Ibrahim *et al*. (2019). They recorded a significant increase of Non-specific EST activity in the case of both combined application and *H. zealandica* infection alone. Later on, last instar larvae of the same insect were infected with EPNs, *H. bacteriophora*, *S. carpocapsae*, *S. scapterisci* and *S. glaseri* by Khater *et al*. (2020). Depending on their results, infection with the concentration 50 IJ of *S. glaseri* led to an initial increase of α-esterase activity which was then significantly decreased later. Infection with *S. carpocapsae* led to a significant decrease of β-esterase activity 12 h post-infection. On the contrary, β-esterase activity increased at the highest concentrations, 24 and 48 h post-infection. Unfortunately, no scientific interpretation was provided for these reported results.

3.2.6. Disturbed Activity of Glutathione S-transferase in Insects:

Glutathione S-transferases (GSTs) constitute a large class of multifunctional intracellular enzymes and are widely distributed in prokaryote and eukaryote, such as animals, insects, plants, and microorganisms (Francis *et al*., 2005). GSTs are known as biotransformation enzymes in all organisms and play a central role in the intracellular material transportation and hormone synthesis (Hayes *et al*., 2005). Also, GST is one of the most important detoxification enzymes present in insects and represents the first of all enzymes associated with insecticide degradation. Its activity has been found to increase in insects resistant to insecticides (Clark, 1990; Papadopoulos *et al*., 2000). For some detail, GST is involved in the detoxification of both endogenous and exogenous xenobiotics, natural and synthetic compounds in insects, *via* glutathione conjugation, dehydrochlorination and glutathione peroxidase activity (Francis *et al*., 2005) to become more water soluble and less toxic (Hyrsl*et al*., 2007; Oruc, 2011; Erdem and Büyükgüzel, 2015). Thus, xenobiotics have increased solubility and are excreted from the insect body by the production of mercapturic acid derivatives (Enayati *et al*., 2005; Li *et al.,* 2007; Ramsey *et al*., 2010).

In addition, GST participates in the cellular antioxidant defenses against oxidative stress, since it contributes to metabolite removal and protection of tissues from damage by free radicals *via* the detoxification of lipid peroxides caused by oxidative stress (Leaver and George, 1998; Papadopoulos *et al*., 2000).It is important for maintaining the homeostasis of oxidation and antioxidant in insects by removing redundant free radicals (Sheehan *et al*., 2001; Wu *et al*., 2013) beside its role as good biomarker to detect exposures to metals, organic pollutants (Yang *et al*., 2002) and pesticides (Tayssee*t al*., 1998). The disintegration inactive poisonous particles with GSTs and ESTs through infections have an opener function in save insects from pathogens (Dubovskiy*et al*., 2012).

According to some results reported in the current literature, GST activity increased or decreased in insects after infection with certain EPN species depending on some factors. After infection of *T. molitor* larvae with different concentrations of EPN *H. beicherriana*, Li *et al*. (2016) determined remarkable enhancement of the GST activity at lower EPN concentrations, but inhibition at higher concentrations. This finding was consistent with a previous study which reported an induction of GST in the *G. mellonella* larvae after infection by *H. beicherriana* (Wu *et al*., 2013). Also, larvae of *G. mellonella* had been infected with the LC_{50} of EPN (*H. zealandica*) and entomopathogenic fungus (*B. bassiana*), separately and

in a combination. GST activity significantly increased in 36 hr, then decreased to 48 hr post-combined infection, in all treatments (Ibrahim *et al*., 2019)**.** Based on the results of Li *et al*. (2022), activity of GSTin larvae of *H. parallela* was almost enhanced during the early period (24 hr) after EPN *H. beicherriana*, Entomopathogenic bacterium *B. thuringiensis* (*Bt*), or EPN+*Bt* combination exposure. Moreover, the enzyme activity of EPN+*Bt* treatment was higher than EPN or *Bt* infection alone. As recorded by Shairra*et al*. (2016b), the activity of GST was significantly enhanced in a dose-dependent manner in *A. ipsilon* larvae after infection with *S. carpocapsae* or *S. scapterisci*. Also, an increased GST activity was observed in a time dependent manner in *S. litura* larvae after infection with *H. indica* (Lalitha *et al*., 2018).

The significantly enhanced activity of GST at early time interval of EPN infection may be the overreactive stress response to the EPNs infection and the overreaction could lead to the death of host insects (Shairra*et al*., 2016b). However, the decreased GST activity 16 h post-infection indicates that EPNs infection may consume GST through detoxification reactions of glutathione-dependent enzymes (Wu *et al*., 2013). In other words, the increase in GST activity in larvae may be due to the detoxification reactions and adaptive responses to neutralize EPN-induced oxidative stress (Li *et al*., 2016).

3.3. EPN Infection Interferes with Activities of the Major Humoral Immunity-Related Enzymes in Insects:

3.3.1. Humeral Immune Defencesin Insects- A Synopsis:

Insects have several defense reactions against the invading pathogens, including the morphological and immunological defenses (Moret and Siva-Jothy, 2003; Kunc *et al*., 2017). The innate immunity-defense strategies can be classified into two major classes, cellular immune reactions and humoral immunereactions (Berger and Jurcova, 2012).Cellular immune response is provided by certain types of the freely circulating hemocytes, whose population increases in response to the microbial pathogenicity, since hemocytes are responsible for the formation of cell aggregates; nodulation, phagocytosis and encapsulation (Chapman, 1998; Hoffmann, 2003; Irving *et al*., 2005). In this regard, the pathogen infection was reported to activate a host of immune activities, most prominent among them being phagocytosis and encapsulation by hemocytes (Hoffmann, 1996). For some details of cellular immune defences in insects, see Lavine and Strand (2002), Kanost*et al*. (2004), Kanost *et al*. (2004), Ribeiro and Brehelin (2006), Strand (2008) and Ghoneim *et al*. (2021).

Humoral innate immune responses in insects involve many antioxidant enzymes and antibacterial proteins produced in the fat body and hemocytes of insects (Wang and Zhang, 2008). In insects, some of the major antioxidant defense enzymes, involved in scavenging of free radicals, are peroxidases, Superoxide dismutases, glutathione peroxidase, catalases, reduced glutathione and glutathione reductase (Mates, 2000; Cytrynska*et al*., 2007; Lalitha *et al*., 2018). In insects, also, there are some secondary metabolites, produced by the EPN-symbiotic bacteria, active against insects, and the pathogenicity of these toxins to insects occurs *via* the suppression of these immune responses in the insect host (Ullah *et al*., 2014). These toxic metabolites result in generation of reactive oxygen species (ROS). These free radicals are highly reactive and result in harmful effects on cells and tissues in the host organism. Living organisms must, therefore, remove or scavenge ROS before cell damage occurs (Feig *et al*., 1994). Also, certain components of the insect immune system produce ROS as a tool to limit microbial growth (Lalitha *et al*., 2018).

It is important to point out that the low levels of ROS are not harmful to living cells and may even perform useful functions, whereas high levels of ROS are dangerous through reactions with many intracellular targets, including proteins, lipids, and DNA. In other words, the lethal process of an Entomopathogenic organism is related to considerably elevated levels of ROS (Wang *et al*., 2001; Wu and Liu, 2012), as well as activity disturbance of some

proteolytic enzymes in the insect host (Grewal *et al*., 2005). However, excess production of ROS and other free radical intermediates produced in response to environmental stress, such as pathogen infections, can cause significant damage to cells due to oxidative stress (Rahman and Macnee, 2000) because ROS-induced damage result in the cell death or sublethal injury, such as mutations, chromosomal aberrations, or carcinogenesis (Wang *et al*., 2001).

EPNs and their symbiotic bacteria collaborate to suppress the immune response of the insect host for achieving a successful infection (Dowds and Peters, 2002). For instance, EPN *Steinernema carpocapsae* and its symbiotic bacterium *Xenorhabdusnematophila* can inhibit the antibacterial peptide immune reaction of insects (Binda-Rossetti *et al*., 2016). In a study, Toubarro*et al*. (2013) found *S. carpocapsae* displaying destructive approaches for host immunity through proteolytic secretion which inhibits host immunological defenses. The EPN-symbiotic bacteria, *Photorhabdus* spp. and *Xenorhabdus* spp. displayed similar lifestyles but have different molecular defensive mechanisms (Goodrich-Blair and Clarke, 2007). The symbiotic bacteria *Xenorhabdus* spp. inhibits the host's immune system by producing a variety of toxins and carrying type III effector molecules that may interfere with the actin cytoskeleton and prevent phagocytosis (Dillman *et al*., 2012). *Photorhabdus* spp. use lipopolysaccharide (LPS) modification to resist the action of the host-derived antimicrobial peptide (AMPs) (Eleftherianos*et al*., 2006), while *Xenorhabdus* spp. prevents induction of insect AMP expression altogether (Istkhar*et al*., 2019). In insects, the pathogenic impacts of symbiotic bacteria and the anti-bacterial resistance mechanisms have been well described, however, EPN-associated defenses are nowadays primarily the focus of research (Sikandar *et al*., 2021).

3.3.2. Effects of EPNs on the Activity of Peroxidase:

From the function point of view, peroxidase (POD) protects the living cells from oxidative damage induced by xenobiotics and pathogenic infection in insects (Zhao *et al*., 2001). Also, Lalitha *et al*. (2018) reported that POD activity was significantly lowin *S. litura* larvaefor 3, 6, 9 and 12 h post-infection with *H. indica*, *i.e*., POD activity did not change in response to the EPN infection. On the other hand, the POD activity in *G. mellonella* larvae infected with *H. beicherriana* gradually increased from 0 to 24 h of treatment, followed by a sharp decrease at 40 h (Wu and Liu, 2012).

Similar result was obtained by Li *et al*. (2016) for the *T. molitor* larvae after infection with different concentrations of EPN *H. beicherriana*, since POD activity quickly increased at higher concentrations after 24 h but decreased later on. Recently, Li *et al*. (2022) found that the activity of PODin larvae of the beetle *H. parallela* was almost enhanced during the early period (24 h) after EPN *H. beicherriana*, *B. thuringiensis* (*Bt*), or EPN+*Bt* combination exposure. However, the enzyme activity was suppressed after infection with the EPN-*Bt* combination for 4 days. This rising and then decline of POD activity may be associated with the persistent infection of EPN, the rapid propagation of its symbiotic bacteria, and the increase of *Bt* intake, which destroyed the cellular structure of the mid-gut and fat body of larvae and hindered the normal physiological metabolism (Vachon *et al*., 2012; Wu *et al*., 2015). In contrast, no fluctuation of POD activity was detected by Abd-El Wahed and Elhadidy (2018) but permanent decrease, since infection of *L. migratoria* 5th instar nymphs with EPN *S. carpocapsae* resulted in a remarkable decrease of POD activity at 24 h post-infection, but a slight decrease of activity at 48 h post-infection.

Apart from EPNs, some authors (Müller *et al*., 2007; Wu *et al*., 2011) reported that the increase in the activity of POD was found in connection with the resistance of insects to pesticides. Also, exposure to chemical pesticides usually results in remarkable increase in POD activity in the cowpea seed beetle *Callosobrochus maculates* (Coleoptera: Chrysomelidae) (Kolawole and Kolawole, 2014). In addition, Elbanna *et al*. (2012) reported

that the POD activity in *S. gregaria* nymphs was altered between rising and declining by entomopathogenic fungus *M. anisopliae* infection.

3.3.3. Effects of EPNs on the Activity of Catalase:

After exposure of an insect to pesticides, catalase (CAT) activity promotes removal of hydrogen peroxide (H_2O_2) and prevention of oxidative damage. Its activity in the tissue surrounding the primary infection site is reported to have a close relation to programmed cell death (Schenk *et al*., 2000). The current literature contains different fluctuations of CAT activity in insects under EPN infection. For instance, Li *et al*. (2016) infected the *T. molitor* larvae with different concentrations of EPNs *H. beicherriana* and observed a quick increase of CAT activity at higher concentrations after 24 h but decreased later. This result was consistent with the result of Wu and Liu (2012), since the activity of CAT in *G. mellonella* larvae infected with *H. beicherriana* gradually increased from 0 to 24 h of treatment, followed by a sharp decrease at 40 hr. In a study of Lalitha *et al*. (2018), a high catalase activity was observed at 6 h exposure of EPN *H. indica* on *S. litura* larvae. Recently, Li *et al*. (2022) found the activity of CAT in larvae of the beetle *H. parallela* almost enhanced during the early period (24 h) of EPN *H. beicherriana*, *B. thuringiensis* (*Bt*), or EPN+*Bt* combination exposure. Then, the enzyme activity was suppressed after infection with the EPN-*Bt* combination for 4 days. These authors tried to explain their result by the rapid propagation of EPN-symbiotic bacteria, and the increase of *Bt* intake, which destroyed the cellular structure of the mid-gut and fat body of larvae and hindered the normal physiological metabolism (Vachon *et al*., 2012; Wu *et al*., 2015). In addition to EPNs, the CAT activity was decreased after exposure of *B. thuringiensis* alone on the *G. mellonella* larvae (Dubovskiy*et al*., 2008).

3.3.4. Effects of EPNs on the Activity of Superoxide Dismutases:

Superoxide dismutase (SOD) is an important enzyme among the antioxidant defense enzymes of insects which are responsible for the scavenging of free radicals. It scavenges superoxide anions and detoxifies them by converting them to H_2O_2 and oxygen. The H_2O_2 is then transformed to the water and oxygen by other enzymes, such as POD, CAT and GPx (Nordberg and Arner, 2001) and the imbalance between oxidative stress and antioxidant responses leads to disease and even death of insects (Felton and Summers, 1995).

A few studies shed some light on the disturbance of SOD activity in insects under stress of the EPN infection. After infection of *T. molitor* larvae with different concentrations of *H. beicherriana*, Li *et al*. (2016) recorded a quickincrease ofSOD activity at higher concentrations after 24 h but the enzyme activity was decreased later on. A few years before this study, Wu and Liu (2012) reported that the SOD activity in *G. mellonella* larvae infected with *H. beicherriana* gradually increased from 0 to 24 h post- treatment, followed by a sharp decrease at 40 h. In the same trend, Li *et al*. (2022) reported that the SOD activity in larvae of *H. parallela* increased during the first 24 h post-infection with *H. beicherriana*, *B. thuringiensis* (*Bt*), or EPN+*Bt* combination. Then, the enzyme activity decreased after infection with the EPN-*Bt* combination for 4 days.

3.3.5. Effects of EPNs on the Activity of Tyrosinase:

Pathogen infection normally activates multiple systemic responses in insect hosts, including phagocytosis and encapsulation by hemocytes (Xia *et al*., 2000; Hassan *et al*., 2016), accompanied with melanization reactions (Hoffmann *et al*., 1996; Söderhäll and Cerenius, 1998). Insects defend themselves against attacking parasites and pathogens *via* the melanin biosynthetic pathway as a necessary mechanism of defense reaction (Sugumaran, 2002) because they do not have antibodies (Hoffmann *et al*., 1996). Tyrosinase (TYR) is often considered as an essential component of invertebrate's immune system. TYR has been known as phenoloxidase for three physiologically important processes (cuticle sclerotization, defense reaction, and wound healing). Through a series of reactions, the pathogen or any foreign organism is encapsulated and often melanized (Sugumaran *et al*., 2000). Including

TYR, melanization is based on the pro-phenoloxidase (pro-PO) cascade, which is a common and generalized response to immune defense (Hoffmann *et al*., 1996). The first step in generating catechol products is the hydroxylation of tyrosine (a monophenol) to produce 3,4-dihydroxyphenylalanine (DOPA, an o-diphenol). DOPA and its derivatives, such as dopamine, are oxidized to their corresponding quinones, which undergo subsequent reactions leading to melanization (Gorman *et al*., 2007).

To investigate the effect of EPN infection on TYR activity in insects, Balasubramanian *et al*. (2010) conducted a study in which they found that a trypsin-like serine protease extracted from secretions of the EPN *S. carpocapsae*could inhibit the TYR activity in *G. mellonella* larvae. According to these authors, their result indicates that the changes of TYR activity in the EPN-infected larvae are context dependent. Moreover, activity of TYRwas significantly enhanced in a dose-dependent course in *G. mellonella* larvae early after infection with *H. beicherriana*. On the other hand, the enzyme activity decreased 16 h post-infection (Wu *et al*., 2013). After infection of the *T. molitor* larvae with different concentrations of *H. beicherriana*, Li *et al*. (2016) found that the TYR activity increased slowly at lower concentrations for 16 h, followed by a slight decrease, and then increasing from 32 to 40 h.

Wu *et al*. (2013) explained the increasing TYR activity in *G. mellonella* larvae infection with *H. beicherriana*by an overreactive stress response to EPNs infection which could lead to death of the insect host, while the decreased TYR activity 16 h post-infection indicated that EPN infection may consume superfluous TYR. For some details, Li *et al*. (2016) suggested that the activity of TYR first increased shortly after the EPN infection to the insect host and then considerably increased in bulk during the mass production of the EPN-symbiotic bacteria released by EPN. These reactions not only prevent the multiplication of the invading IJs of the EPN but also prevent the damage caused by it (Sugumaran, 2002). In addition, when immune defense is expressed in the infected insect at TYRhigh levels, it is often traded off against other fitness parameters (Moret, 2006) because immune effector systems are costly to maintain and use while beneficial against parasitic attacks (Sugumaran, 2000).

In general, the increasing activities of antioxidant enzymes in *G. mellonella* larvae after infection with EPNs suggested that EPNs' infection increases the level of oxidative stress and antioxidative responses in larvae, and the oxidative damage contributes to the cell death(Wu and Liu, 2012). Some years later, Li *et al*. (2016) suggested that the host antioxidative response and detoxification reactions played a central role in the defensive reaction to EPNs, and that this stress which was reflected by the higher-levelenzymes activity contributed to the death of hosts.

3.3.6. Effects of EPNs on the Activity of Immune Response-MediatedPhenoloxidasein Insects:

In invertebrate immunology a complex array of host defenses has been reported including phagocytosis and melanization (i.e., synthesis and deposition of melanin around the pathogen) (Bulet*et al*., 2004; Nappi and Christensen, 2005). The innate immune response in insects involves both humoral and cellular components. Humoral responses comprise the antimicrobial melanizing enzyme, phenoloxidase (PO) (Meister and Lagueux, 2003; Shelby and Popham, 2006; Zhao *et al*., 2007). The melanization is achieved as a consequent to the activation of the inactive proPO to PO (Cerenius and Soderhall, 2004; Shelby and Popham, 2006; Cytrynska*et al*., 2007). This enzymatic activation requires protease cascades triggered by the detection of specific microbial patterns (Cerenius*et al*., 2008; Eliáš *et al*., 2020). Shortly, melanization response in insects, as a humoral immune defence, involves the deposition of melanin to invading pathogens. The melanization reaction needs PO which

catalyzes the oxidation of mono- and diphenols to orthoquinones (Eleftherianos and Revenis, 2011; Lu *et al*., 2014).

It may be important to shed some light on the enzyme PO in some detail. It is a copper containing enzyme (Lu and Jang, 2007). In insecthaemolymph, PO is responsible for melanotic immune responses that occur immediately against invading pathogenic microbes into insects (Castillo *et al*., 2011). For some detail, see the recent review of Mahanta*et al*. (2023). However, PO participates in encapsulation, clotting of haemolymph, wound healing (Cerenius*et al*., 2008) and stimulates phagocytosis. Also, PO is involved in other physiologically important processes, such as sclerotization of the cuticle, an essential step for the survival of all insects (Sugumaran *et al*., 2000). PO is produced in response to infection by activated hemocytes of the insects (Lavine and Strand, 2002; Kanost and Gorman, 2008; Castillo *et al*., 2011; González-Santoyo and Córdoba-Aguilar, 2012). Therefore, PO activity is a good indicator of protective response against invading entomopathogens and parasitoids in insects (Freitak*et al*., 2007). Furthermore, PO has main role for melanogenesis in the immune system of insects for converting the phenols to short lived chemically reactive quinones, which subsequently polymerize to form melanin coat around the invading pathogen (Cerenius and Soderhall, 2004; Eleftherianos and Revenis, 2011; Castillo *et al*., 2011) and generating toxic radicals (Shelby and Popham, 2006).

For some details, the enzyme PO is the active form of zymogenic proPO. Although proPO can be activated in the insect plasma by proteolytic cleavage at a specific site near its amino terminus by serine proteases, the zymogen is localized generally in the oenocytoids, plasmatocytes, spherulocytes and granulocytes (Lavine and Strand, 2002; Ling *et al*., 2005; Neuwirth, 2005). In the defense process, peptidoglycan recognition protein binds to its respective elicitors and results in the production of inactive proPO (Eleftherianos and Revenis, 2011). Activation of proPO to produce PO occurs immediately against invading microbes in the haemolymph of insects in response to the immune challenge (Marmaras *et al*., 1996; Gillespie *et al*., 1997), such as the melanin formation around the invading pathogens (Christensen *et al*., 2005; Xue *et al*., 2006) that participate in sequestrating and/or killing the pathogens (Nappi and Vass, 2001).

As reported in the current literature, a few studies investigated the infectious effects of EPNs on the POactivity in insect hosts (Walter *et al*., 2008; Kramarz *et al*., 2016). Injection of *H. bacteriophora* into the 3rd instar larvae of the flesh fly *Parasarcophagasurcoufi* (Diptera: Sarcophagidae) significantly suppressed the haemolymph PO activity even in the presence of the activators laminarin, alpha-chymotrypsin and methanol. This suppression was dose-dependent and reached its maximum at 30 h post-injection (Ayyad *et al*., 2001). Shairra*et al*. (2016a) infected the *P. gossypiella* larvae with the EPN *S. riobrave* or *H. bacteriophora* and found decreasing PO activity followed by increased activity, indicating the important role of PO in defeating the immune system in larvae of *P. gossypiella*. At the same year, results of Shairra*etal*. (2016b) revealed that PO activity was significantly enhanced in a dose-dependent manner in haemolymph of *A. ipsilon* larvae infected with EPN *S. carpocapsae* or *S. scapterisci*. The same authors interpreted their result by the overreactive stress response of larvae to the EPNs infection. This overreaction often leads to death of the insect host.

Ebrahimi *et al*. (2014) recorded an increase of PO activity in the haemolymph of *S. carpocapsae*-injected larvae of Colorado potato beetle *Leptinotarsa decemlineata* (Coleoptera: Chrysomelidae). They found this increase in an EPN dose-dependent manner, and the increasing EPN concentration led to increased PO activity which was coincident with the appearance of EPN-symbiotic bacteria in the haemolymph of these larvae. Abd-El Wahed and Elhadidy (2018) reported that the infection of *L. migratoria* 5th instar nymphs with EPN *S. carpocapsae* resulted in increasing PO activity, 24 & 48 h post-infection. Depending on

the results of Ebrahimi *et al*. (2018), PO activity assay revealed higher levels of the enzyme activity in EPN-injected *H. armigera* larvae, which suggested the *H. armigera* PO activation by *S. feltiae* infection. Releasing the symbiotic bacteria and increasing the bacterial cells in haemolymph of *H. armigera* during the experimental time interval were reasonable explanation for increasing trend of PO activity in nematode-injected insects. Also, similar results were obtained by Yang *et al*. (2012) in larvae of the same insect.

On the contrary, Brivio *et al*. (2002) reported that the infection of *G. mellonella* larvae with *S. feltiae* led to the inhibition of PO activity. They showed that IJs of *S. feltiae* induced the speedy suppression of PO tend to avoid host humoral encapsulation. Also, infection of the 4th larval instar larvae of *A. ipsilon* with EPNs *H. zealandica* and *S. abbasi* led to decreasing PO activity in the infected larvae (Ibrahim *et al*., 2015). Reduction of the enzyme activity was remarkable in *H. zealandica*-infected larvae may be due to the highly toxic compounds released by the *Photorhabdus* symbiotic bacteria which induce PO inactivation in the haemolymph of *A. ipsilon* larvae (Ibrahim *et al*., 2015). In Egypt, also, Ibrahim *et al*. (2019) investigated the effects LC_{50} concentrations of EPN (*H. zealandica*) and entomopathogenic fungus (*B. bassiana*), separately and in a combination, on immune and antioxidant enzymes in larvae of *G. mellonella*. Depending on their results, the combination of *H. zealandica*+*B. bassiana* or *H. zealandica* alone exhibited a significant suppressive effect on the PO activity over time.

To investigate the correlation between proPO and PO, Brivio *et al*. (2002) reported that the *S. carpocapsae*-secreted chymotrypsin proteases can inhibit proPO leading to reduced PO activation and encapsulation in the *G. mellonella* larvae, while *S. feltiae* induces proPO inactivation in larvae by down-regulating the proPO pathway. Similar result was obtained by Balasubramanian *et al* (2009), since EPN *S. abbasi* induces poPO inactivation in *A. ipsilon* larvae. Depending on the results of Lalitha *et al*. (2018), a significant increase in PO levels were observed in haemolymph of *S. litura* larvae suggesting that *H. indica* cell wall components are recognized by ProPO and results in PO activation.

Summary Points:

* The main body metabolites (proteins, lipids and carbohydrates) in insect larvae were reported to be disrupted by the infection with EPNs. The interaction between nematode and insect larvae appeared to be primarily nutritional, since growth of the EPN proceeds while the nutritional requirements of the host larvae deteriorate, i.e., the host become in a state of physiological starvation. The protein content in haemolymph of larvae is usually reduced by the EPN infection suggesting the main cause of the host quick death is the suppression of immune response of the infected larvae.
* Many results revealed the reduction of lipid content, regardless of the EPN species. This may be due to the shift in energy metabolism towards lipid catabolism as a result of physiological stress caused by EPNs. Also, the carbohydrate content in EPN-infected insects was reported to decrease due to the accelerated glycogenolysis and/or impaired glycogenesis.
* Not only the main body metabolites but also the food consumption and metabolic efficiencies of insects have been disrupted by EPN infection. The considerable reduction of the food utilization efficiencies of the insect larvae after infection with EPN suggested that most of ingested or digested food was metabolized for energy production, and it is likely that the major portion of this energy was utilized for defense against the invading pathogens.
* Some EPNs adversely affect the developmental physiology, such as the developmental durations and some adult performance parameters, as well as the major reproductive parameters, fecundity and egg fertility.
* In respect of the major digestive enzymes in insects, activities of different carbohydrate hydrolyzing enzymes, such as amylase, trehalase and invertase, were disturbed by EPN infections.

* Concerning protein hydrolyzing enzymes, very few studies revealed the inhibition of protease activity in some insects after infection with certain EPN species which could be due to the symbiotic bacteria start to digest the proteins of the insect body 16 hr post-infection.
* In connection with lipid hydrolyzing enzymes, increasing lipase activity was observed in insects after EPN infection. This reported result can be understood in view of the activity of EPN- symbiotic bacteria which secrete various enzymes, such as hemolysis, lipases, and proteases, that contribute to pathogenicity or nutrient acquisition for the bacterium and its nematode host, lipase activity was dramatically boosted.
* The detoxification enzymes in insects have many functions for repairing the physiological processes, detoxifying pathogenic products, and metabolizing the biologically active compounds. In insects, also, the detoxification can be achieved by different families of enzymes. Some authors reported superoxide dismutase, peroxidases and catalases as antioxidant enzymes and carboxylesterase, glutathione S-transferase and acetylcholinesterase as detoxifying enzymes, since insects are known to use antioxidants and detoxifying enzymes in their immune systems as defense reactions against pathogen threats.
* With regard to disturbed activities of the detoxifying enzymes, phosphatases, in insects by the EPN infection, increasing activity of acid phosphatase (ACP) in the EPN-infected larvae may indicate a physiological adaptability to combat the oxidative stress or may be due to the phagocytosis of certain hemocytes to the invading EPNs. In contrast, decrease of ACP activity can be due to the inability of the cell to undergo enzymatically controlled reactions under nematode infection, or may be due to the reduced phosphorus liberation for energy metabolism and decreased rate of metabolism, as well as decreased rate of transport of metabolites. In addition, there are many reported results of increasing alkaline phosphatase (ALP) activity in several insects as response to the infection with certain EPNs. On the contrary, ALP activity in larvae of some insects was reduced after infection with certain EPNs.
* Dealing with the disturbed activities of transaminases in insect larvae by EPNs, decreasing activities of these enzymes may be attributed to the significant decline in the free amino acids content, the quantum of which directly influences the activity of transaminases at the time of protein synthesis. Also, reduction of transaminase activity may be due to the interference of the EPNs with the hormonal regulation of protein synthesis and neurosecretory hormones involved in the regulation of transaminase levels.
* Few studies investigated the effects of EPNs on the activity of acetylcholinesterase (AchE) in insect larvae. Many studies recorded the increasing enzyme activity, but few studies recorded decreasing activity of this enzyme. Increased AchE activity in insects may be the overeactive stress response to the EPN infection. This overreaction often leads to death of the insect. Also, the increase in AchE activity may be correlated with secretions produced by the nematode-bacterium complex.
* In addition to the role of Carboxylesterase (CarE) in insecticide resistance, some studies reported the enhancement of its activity early after infection with EPNs and it was inhibited later on. It seems that the insects overreacted to the EPNs infection by enhancing the CarE activity first, indicating that many lipids would be disintegrated, which would damage organs and tissues, and lead to the death of host insects. Then, the EPNs-infection response would consume the CarE resulting in the decreased CarE activity.
* Esterases (ESTs) constitute a large class of enzymes. Most enzymes of this group are important in metabolism because they can break ester bond through hydrolysis. Also, some ESTs play a critical role in the detoxification of synthetic chemicals. Only few studies focused on the impacts of EPNs on the activities of ESTs in insects.
* Glutathione S-transferase (GST) is involved in the detoxification of both endogenous and exogenous xenobiotics, natural and synthetic compounds in insects. In addition, GST

participates in the cellular antioxidant defenses against oxidative stress. GST activity increased or decreased in the insect haemolymph after infection with certain EPN species depending on some factors. The enhanced activity of GST at early time interval of EPN infection may be the overeactive stress response to the EPNs infection while the decreased activity 16 h post-infection indicates that EPNs infection may consume GST through detoxification reactions of glutathione-dependent enzymes.

* Some research works have been conducted aiming at the understanding of physiological and biochemical mechanisms involved in the insect infection. Insects have several defense reactions against invading pathogens. The innate immunity-defense strategies can be classified into two major classes: cellular and humoral. Humoral innate immune responses in insects involve many antioxidant enzymes and antibacterial proteins produced in the fat body and hemocytes of insects. Some of the major antioxidant defense enzymes are peroxidases, Superoxide dismutases, glutathione peroxidase, catalases, reduced glutathione and glutathione reductase.

* Peroxidase (POD) protects cells from oxidative damage induced by xenobiotics and pathogenic infection in insects. Some studies reported rising (or enhancement) during the early period (24 hr) and then declination (or inhibition) of POD activity in insects after infection with EPNs. Other studies reported continuous decrease of the enzyme level.

* The activity ofCatalase (CAT) in the tissue surrounding the primary infection site is reported to have a close relation to programmed cell death. Some studies reported increasing CAT activity (enhanced) in insects at early time interval (6-24 hr) post-infection with EPNs, but decreased (inhibited) activity some days later.

* Superoxide dismutase (SOD) is an important enzyme among the antioxidant defense enzyme EPNs butts which are engaged in the scavenging of free radicals. A number of studies shed some light on the altered activity of SOD in insects under stress of EPN infection.

* Tyrosinase (TYR) is often considered as an essential component of invertebrate's immune system. TYR has been known as phenoloxidase for three physiologically important processes (sclerotization, defense reaction, and wound healing). The early increasing TYR activity in the EPN-infected larvae may be due to an overreactive stress response to EPNs ending in the insect death, while decreased TYR activity 16 hr post-infection indicate that EPNs infection may consume superfluous TYR.

* Among the necessary components of the humoral innate immunity in insects is Phenoloxidase (PO) via catalyzing the biosynthesis of quinones and other reactive intermediates to eliminate the invading pathogens and parasites. Also, PO is involved in other physiologically important processes, such as sclerotization of the cuticle, an essential step for the survival of all insects. Therefore, PO activity is a measure of protective response against invading microbes in insects.

Conclusions and Prospectives:

As clearly shown in the present review, different EPNs exert various suppressive actions on the innate immune defenses of insects, while the infected insects try to overcome these stresses by several humoral immune defenses, reflecting on the disruption of different physiological and biochemical processes, including the intermediary metabolism, detoxifying enzymes and antioxidant enzymes. The disruptive effects of the EPNs on insects have suggested the potential of these entomopathogens for pest control. However, some points of research need more investigation in future, such as the link between humoral immunity defenses and cellular immunity defenses to understand the defense integration in insects against EPNs.

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