J. Entomol. Res. Soc., 23(3): 225-238, 2021 *Review Article*
Doi: 10.51963/jers.v23i3.2016 *Online ISSN:2651-3579*

Insecticide Resistance in the Brown Planthopper, *Nilaparvata lugens* (Stål): Mechanisms and Status in Asian Countries

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ABSTRACT

The brown planthopper, *Nilaparvata lugens* (Stål) is a destructive rice pest found in almost all the rice-growing areas across the globe. In pest management strategies, insecticides are the vital element to control this insect pest. But recently their heavy use poses a risk of control failure because of the development of insecticide resistance. Quick insecticide resistance development nature in *N. lugens* intrigued scientists to understand the complex resistance mechanism(s), side by side pledge the importance of regular monitoring to know the trend of resistance development. Resistance mechanisms like, target-site insensitivity and enhanced activity of detoxifying enzymes, have been extensively studied and identified in governing the resistance development of *N. lugens*. Both the field collected and laboratory selected pest populations were tested against commonly used insecticides to detect insecticide resistance ratio. In this review, recent findings of resistance mechanisms, candidate genes those contribute in resistance development have been summarized. We also provide an insight into the metabolic resistance mechanisms that confer significant levels of resistances and the current status of insecticide resistance in *N. lugens*. This review will help to get a clearer view on present research directions of insecticide resistance in *N. lugens*.

Key words: Nilaparvata lugens, insecticide resistance, monitoring, metabolic mechanisms.

Datta, J. & Banik, S.C. (2021). Insecticide resistance in the brown planthopper, *Nilaparvata lugens* (Stål): mechanisms and status in Asian countries. *Journal of the Entomological Research Society*, 23(3), 225-238.

INTRODUCTION

Brown planthopper, *Nilaparvata lugens* (Stål) (Hemiptera: Delphacidae) is a major rice pest that causes significant losses in rice-growing areas (Masaya et al, 2009). Since 2003, many Asian countries have seen frequent outbreaks of *N. lugens* (Bottrell & Schoenly, 2012). Chemical control is the key element of integrated pest management strategies to control rice insect pests (Min, Lee, Choi, Lee, & Kwon, 2014). Because of higher efficiency, neonicotinoid is widely used to control many insect pests including *N. lugens* (Matsuda, Ihara, & Sattelle, 2020; Datta et al, 2021a). However, it has developed low to moderate levels of resistance to neonicotinoids. Overdose and constant use of insecticides considers as the key reason for the fast resistance development in *N. lugens* (Matsumura et al, 2018).

Research on insecticide resistance in *N. lugens* has been doubled in recent years, and studies were attempting to explain complex mechanisms conferring resistance. The study of insecticide resistance mechanisms is vital to manage resistance problems, to reduce the threat of pest outbreak and to introduce more improved control measures. Numerous resistance mechanisms have been found governing insect resistance to insecticides (Garrood et al, 2016). Among the two mostly reported resistance mechanisms, the enhanced metabolic detoxification of xenobiotics has been commonly studied in *N. lugens* (Latif, Omar, Tan, Siraj, & Ismail, 2010). Increased activities of detoxifying enzymes have been constantly found in resistant *N. lugens*. Through gene amplification it has been proved that multiple resistance genes are directly correlated with enhanced detoxifying enzyme activities (Hamada, Stam, Nakao, Kawashima, & Banba, 2020). Cytochrome P450 monooxygenase (P450) displayed significant roles in conferring insecticide resistance in *N. lugens* in response to neonicotinoids (Hamada et al, 2020). Functional analysis through RNA interference (RNAi) confirmed the function of multiple P450 genes (Jin et al, 2019). The levels of enhanced detoxifying enzyme activities and the expression levels of the genes encoded for the enzymes vary with the insecticide resistance levels (Mao et al, 2020).

Currently, *N. lugens* developed resistance to frequently used insecticides and there are threats of future resistance development to less used insecticides (Fujii et al, 2020; Matharu & Tanwar, 2020). Previous findings suggest extremely higher levels of resistance to imidacloprid, a principal neonicotinoid insecticide, and potentiality to develop resistance to other insecticides of the same group (Datta et al, 2021a). This review mainly focuses metabolic resistance mechanism as one of the main mechanism to confer insecticide resistance in *N. lugens*. Side by side, the status of resistance to commonly used insecticides developed in this pest has been shortly described.

Nilaparvata lugens a destructive pest of rice

One of the major destructive dominant herbivore of rice is *N. lugens* that is found in all rice-growing areas of Indonesia, Thailand, India, Japan, Vietnam, China, Bangladesh, Solomon Island and north-eastern Australia, the Philippines, and Malaysia (Masaya et al, 2008; Latif et al, 2010; Ali et al, 2014; Hereward et al, 2020). The long distance migratory behavior and population development patterns sometimes make the control measure more complex and most of the rice field of different places became

vulnerable to the pest (Khoa, Thang, Liem, Holst, & Kristensen, 2018). It damaged rice plant by sucking sap during different growth stages of rice plant, which caused wilting and drying, known as "hopper-burn" and it also, transmits several viral diseases (Liao et al, 2019). The outbreaks of *N. lugens* in several rice producing countries have frequently occurred in the last few decades, which is threatening food security for the growing populations (Bottrell & Schoenly, 2012).

Evolution of insecticide resistances in *N. lugens*

Resurgence of *N. lugens* was thought to be associated with different factors likely use of synthetic insecticides, fertilizers and susceptible rice varieties (Uddin, Islam, Jahan, Ara, & Afrin, 2020). Precautions have been taken to control this pest and a significant amount of money have been invested to improve pest control strategies, for instance, in Indonesia alone 100 million US dollar have been invested to control this pest per year (Cheng, 2015). However, the investments to improve control programs sometimes failed to uphold the destruction of rice yield as pest outbreaks in recent years occurs in some Asian countries. Chemical control became the only means to control this destructive insect pest in rice farming practices and since then the use of insecticides considers as the vital element to control this pest (Bottrell & Schoenly, 2012). However, heavy use of common insecticides poses enormous risks not only to environmental elements but the reduced toxicity of insecticides against *N. lugens* (Mu et al, 2016).

Insecticide Resistance Action Committee (IRAC) defined insecticide resistance as the repeated failure of a chemical product to damage insect pest population in an expected level even after applying recommended doses (Sparks & Nauen, 2015). Evolution of insecticide resistance in insect pest has become a threat in choosing efficient insecticide for its management (Bolzan et al, 2019). Even after the continuous use of insecticides, farmers witnessed the resurgence of *N. lugens*; studies later find out the development of low to high level of resistance in *N. lugens* (Cheng, 2015; Uddin et al, 2020). The demand and use of synthetic insecticides to control *N. lugens* never been clogged but increased proportionately in some places, which extends the resistance problems. It has been reported that *N. lugens* field populations already developed moderate to extremely high level of resistance to imidacloprid, thiamethoxam, buprofezin, dinotefuran (Liao et al, 2021). In addition, the cross-resistance between different insecticides among the field populations is also posing a threat to select competent insecticide classes to control BPH (Mu et al, 2016).

Mechanism of insecticide resistance

Development of insecticide resistance relies on particular resistance mechanisms of insects. Four resistance mechanisms have been reported in insect pests, however, according to previous studies two major mechanisms are mainly contributing in developing resistance in *N. lugens*, target-site modifications and metabolic resistance. Majority of the research described metabolic resistance mechanisms as the principal mechanism to induce resistance in this pest (Mao et al, 2020). Here, both of the reported mechanisms are discussed, although metabolic mechanisms cover most of the portion of this review.

Target-site insensitivity

Several insecticides affect specific target sites of insect nervous system. It has been found that resistant insect shows modifications in their target sites to confer resistance against particular insecticide (Steinbach et al, 2015). In two nicotinic acetylcholine receptor (nAChR) subunits, point mutations (Y151S) have been identified in association with imidacloprid resistance in *N. lugens* (Zewen et al, 2005). However, the mutations in target site have only been found in laboratory selected imidacloprid resistant-strain and never been reported in resistant field populations of *N. lugens* (Zewen et al, 2005; Liang et al, 2018; Sanada-Morimura et al, 2019). For this reason most of the recent research only emphasizes complex metabolic resistance mechanisms that found both in lab selected strain and field collected *N. lugens*. These findings shed light to study insecticide resistance mechanisms in this pest in response to distinct insecticide classes.

Metabolic resistance mechanism

Metabolic resistance is the principal mechanism and widely studied topic in *N. lugens.* Its resistance evolution to common insecticides is mostly attributed to the enhanced detoxification of enzymes, and expression of resistance genes encoded for detoxifying enzymes (Wen, Liu, Bao, & Han, 2009). The metabolic resistance mechanisms reported in previous findings have been summarized.

Metabolic enzyme activities

The involvement of a metabolic enzyme in detoxifying insecticide has proved by measuring the enhanced levels of detoxifying enzyme activities in insects. The elevated activities of metabolic enzymes P450, esterases (EST) and glutathione S-transferases (GST) have been reported in several insect species resistant to insecticides (Bass & Field, 2011; Liang et al, 2018). Through the synergistic and enzymatic assay, increased activity of detoxifying P450 enzyme has been found in many insects in response to neonicotinoids insecticides (Chen, Shan, Liu, Shi, & Gao, 2019). Similarly, insecticide resistance of *N. lugens* against different insecticides is mostly controlled by increased enzyme activity, especially P450 enzyme. The level of P450 was significantly high in *N. lugens* resistant to imidacloprid, thiamethoxam, and dinotefuran compare to susceptible pest (Sun, Gong, Ali, & Hou, 2018). Detection of enhanced P450 activities in resistant *N. lugens* strain, suggesting P450-mediated detoxification occurs in imidacloprid-, thiamethoxam-, and dinotefuran-resistant strains. In contrast, significantly increased activities of two detoxifying enzymes, P450 and EST, were found in nitenpyram and sulfoxaflor selected strain, but P450 might be the major detoxifying enzyme (Liao et al, 2019). Although the finding of enzymatic assay was consistent with the synergistic assay, characterization of gene expression and functional validation of specific gene are needed to confirm the xenobiotic mechanism in response to nitenpyram and sulfoxaflor. The elevated levels of EST activities have been reported higher in chlorpyrifos-resistant strain compare to susceptible strain of *N. lugens* (Lu et al, 2017). This report suggests that enhanced EST activity could account for resistance to organophosphate insecticides.

Characterization of resistance genes

Studies have successfully characterized gene expression that revealed significant information of metabolic enzymes associated with detoxification of insecticides (Table 1). A number of metabolic resistant genes individually and/or in group have been reported overexpressed in resistant *N. lugens* through gene amplification, transcriptional up-regulation and genome sequencing (Zhang et al, 2016a; Xu et al, 2017). Three major metabolic detoxification genes have been reported in *N. lugens* that involves in the detoxification of insecticides (Liang et al, 2018). Among them P450s are considered as the principal contributor to confer resistance that found in all the living organisms (Wang et al, 2018). Reported P450 genes are belonged to microsomal CYP4, CYP6, CYP9, and mitochondrial CYP12 families and are mostly correlated with the resistance development to neonicotinoids (Feyereisen, 1999; Scott, 1999). Many researchers have also been found several P450s involvement in *N. lugens* resistance to distinct classes of insecticides. Overexpression of one or multiple P450 genes have been reported in this pest resistance to imidacloprid, thiamethoxam, dinotefuran, buprofezin, nitenpyram, sulfoxaflor, clothianidin and etofenprox (Pang et al, 2014; Garrood et al, 2016; Liao et al, 2021; Datta et al, 2021b). Similarly, the up-regulation of esterase gene *NlCarE* was found related to chlorpyrifos resistance in *N. lugens* (Lu et al, 2017). It is obvious that P450s as the superfamily has repeatedly been verified that confer insecticide resistance in *N. lugens*. Recent advances in research have been very useful to generate knowledge about the resistance genes those are significantly contributing in insecticide metabolism in *N. lugens*.

Functional validation of resistance genes

Bao et al, (2016) characterized imidacloprid metabolism by determining *CYP6ER1* and *CYP6AY1* expression in vitro through recombinant P450 proteins. Similarly, using the recombinant P450 proteins, enzymatic activities of five P450s were determined to analyze their roles in developing resistance to imidacloprid (Zhang, Yang, Sun, & Liu, 2016b). Among the five P450 proteins, the fastest metabolite formation was observed in incubation with *CYP6CW1*, *CYP6AY1*, *CYP6ER1*, and *CYP4CE1* (Zhang et al, 2016b). These approaches confirmed the contribution of these genes in resistance development in *N. lugens*.

The overexpression of metabolic detoxification genes displayed its significance in resistance development in *N. lugens*, which implies the importance to characterize individual gene function involving in resistance. Studying the metabolic mechanisms has been improved in this genomic era with the advancement of the molecular tools and techniques including gene silencing technique, RNAi and CRISPR/Cas9 (Unniyampurath, Pilankatta, & Krishnan, 2016; Zhu, Chereddy, Howell, & Palli, 2020). Silencing of overexpressed P450 gene, *CYP6ER1*, in lab strain of *N. lugens* increased susceptibility to imidacloprid, thiamethoxam, dinotefuran, nitenpyram and sulfoxaflor, which demonstrated the involvement of *CYP6ER1* as the functional gene in resistance development (Jin et al, 2019; Liao et al, 2019). Although most of the findings outlined *CYP6ER1* as the key P450 gene contributes in conferring

insecticide resistance in *N. lugens*, overexpressed *CYP6AY1* is another important P450 gene reported by several authors. The *in vivo* study through RNAi reduced the mRNA levels of *CYP6AY1* in imidacloprid resistant strain and increased the mortality rate of the pest after the imidacloprid application (Bao et al, 2016; Ding et al, 2013). This indicated that *CYP6AY1* dsRNA feeding successfully suppressed insecticide resistance to imidacloprid and confirmed the role of *CYP6AY1* gene in insecticide resistance. The overexpression of P450 genes has also reported in *N. lugens* resistant to pyrethroid insecticides. Multiple P450 genes were silenced through RNAi that cause major changes in resistance levels in BPH against etofenprox, a non-ester pyrethroid insecticide (Sun, Yang, Zhang, & Liu, 2017). The functional analyses of resistance genes by knocking down of multiple genes have considerably extended our understanding on the complex mechanisms of conferring resistance to different group of insecticides. Additionally, the expression level of *NlCarE* was significantly reduced after dsRNA injection in chlorpyrifos resistant *N. lugens* (Lu et al, 2017).

Table 1. Genetic characterization of insecticide resistance mechanism in *Nilaparvata lugens*.

Insecticide	Population/Strain	Methods	Resistance gene(s)	Reference
Imidacloprid[1]	Field	qRT-PCR	*CYP6ER1*	Garrood et al, (2016)
Imidacloprid	Field	qRT-PCR, RNAi	*CYP6ER1, CYP6AY1*	Bao et al, (2016)
Imidacloprid, Thiamethoxam[1], Dinotefuran[1]	Lab	qRT-PCR, RNAi	*CYP6ER1*	Sun et al, (2018)
Imidacloprid	Lab	qRT-PCR, RNAi	*CYP6ER1, CYP6AY1, CYP6CE1, CYP6CW1*	Zhang et al, (2016b)
Imidacloprid	Field	qRT-PCR	*CYP6ER1, CYP6AY1, CYP6CS1*	Zhang et al, (2016a)
Imidacloprid	Field	qRT-PCR, RNAi, transgenic[5]	*CYP6ER1*	Pang et al, (2016)
Imidacloprid	Lab	qRT-PCR, RNAi	*CYP6AY1*	Ding et al, (2013)
Imidacloprid, Buprofezin[2]	Field	qRT-PCR	*CYP6AY1*	Pang et al, (2014)
Imidacloprid	Lab	qRT-PCR, RNAi	*CYP6ER1*	Yang et al, (2016)
Nitenpyram[1]	Lab	qRT-PCR, RNAi	*CYP6ER1*	Mao et al, (2019)
Sulfoxaflor[1]	Lab	qRT-PCR, RNAi	*CYP6ER1*	Liao et al, (2019)
Chlorpyrifos[3]	Lab	qRT-PCR, RNAi	*NlCarE*	Lu et al, (2017a)
Clothianidin[1]	Lab	qRT-PCR, RNAi	*CYP6ER1*	Jin et al, (2019)
Etofenprox[4]	Lab	qRT-PCR, RNAi	*CYP6FU1, CYP425A1,CYP6AY1*	Sun et al, (2017)
Imidacloprid, Thiamethoxam, Dinotefuran, Clothianidin[1], Buprofezin	Field	qRT-PCR	*CYP6AY1, CYP6ER1*	Liao et al, (2021)
Imidacloprid, Thiamethoxam, Dinotefuran, Buprofezin	Field	qRT-PCR	*CYP6ER1*	Datta et al, (2021b)

[1]Neonicotinoids, [2]Insect growth regulator, [3]Organophosphate, [4]Pyrethroids, [5]Transgenic approach utilizing the GAL4/UAS system of *D. melanogaster*

The *Drosophila* transgenic technique is another approach to determine functions of genes in insect resistance to insecticides (Daborn et al, 2012; Pang et al, 2016). The expression of *CYP6ER1* of *N. lugens* in *Drosophila* evolved significant levels of resistance to imidacloprid compare to dinotefuran for the variant of *CYP6ER1* gene (Hamada et al, 2020). This provides important information on the *in vivo* metabolism of imidacloprid resistance by the variants of *CYP6ER1*.

The metabolic resistance mechanism has been depicted with the possible transcription factors regulating gene expression in Fig. 1. Several signaling pathways were found to mediate the up-regulation of detoxification enzymes in insects and play a key role in metabolic resistance to insecticides (Amezian, Nauen, & Le Goff, 2021). The signaling pathways includes transcription factors (TF) namely, cap "n" collar (CncC), musculoaponeurotic fibrosarcoma (MaF), aryl hydrocarbon receptor (AhR), G-protein coupled receptor (GPCR) (Amezian et al, 2021). The expression of two P450 genes contributes to insecticide resistance in *Drosophila* regulated by the transcription factors CncC and Maf (Gaddelapati, Kalsi, Roy, & Palli, 2018; Bo et al, 2020). However, little is known about these gene regulatory factors in gene expression in insects. Further studies are needed to describe the principal regulatory routes of detoxification gene expression in *N. lugens*. It is necessary to clarify what are the specific functions of those genes, what is the exact number of genes, how the genes are correlated with insecticide resistance ratio, and what are the functions that regulate the overexpression of resistance genes.

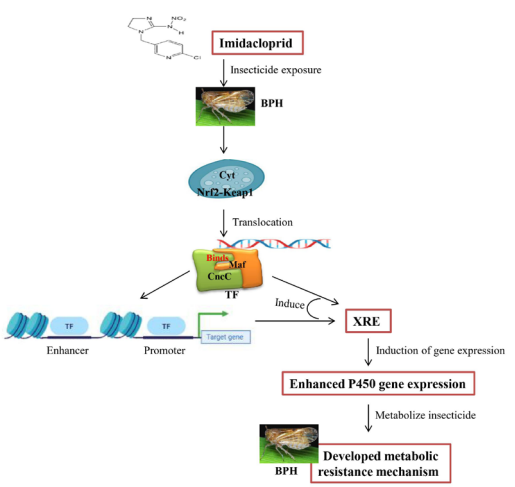

Fig. 1. Flowchart of the development of metabolic resistance mechanism in BPH started in cytoplasm of insect cell. Here, imidacloprid represents the neonicotinoids insecticide group. Through translocation Nrf2 with Keap1 transferred to nucleus. Cyt-cytoplasm; Nrf2-nuclear factor erythroid 2; Keap1-kelch-like ECH-associated protein 1 pathway; XRE-xenobiotic response element. The description of transcription factors and their mechanism in insect pests may found in Palli, 2020.

Current status of insecticide resistance

Since the first outbreak of *N. lugens*, the pest distribution and the population development of the pest has been frequently reported in many studies (Bottrell

& Schoenly, 2012). Additionally, the status of the insecticide resistance has been monitored by different authors, providing details information, which would help forecast pest outbreak hence to improve pest management strategies (Liao et al, 2021). The insecticide resistance status in *N. lugens* has been detected either by topical application of insecticides or by rice stem dipping method (Priyadharshini, Muthukrishnan, Sathiah, & Prabakar, 2020). Studies used field collected pest populations to detect insecticide resistance, which helped to know the exact scenario of the levels of resistance. In contrast, laboratory selected strain has been used to monitor pests ability to develop resistance in controlled condition, to provide information on cross-resistance among insecticides and to compare with field-evolved resistance. The resistance ratio of *N. lugens* to commonly used insecticides reported during 2011 to 2021 has been presented in Fig. 2. The data was collected from multiple studies and the resistance ratio to tested insecticides has been summarized (research findings from where the data was extracted mentioned in Supplementary file).

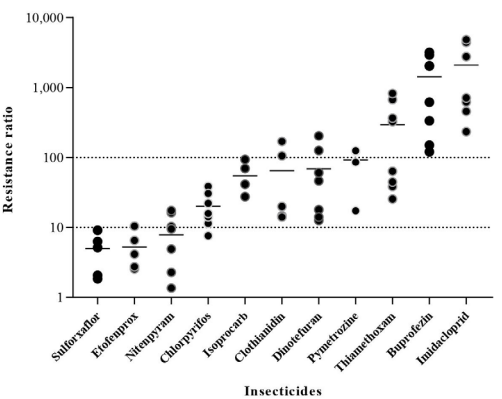

Fig. 2. Previously reported resistance ratio of *Nilaparvata lugens* field populations to several tested insecticides. The resistance ratio (ranges and calculation) was described by Wang et al, (2018). Data of resistance ratio of *N. lugens* field populations is summarized from eighteen different research articles published during 2011-2020.

Resistance to organophosphates and carbamates

Organophosphates and carbamates insecticides target AChE inhibitor of small brown planthopper and have been using to control the pest after the World War II (Kwon, Kim, Jeong, & Lee, 2019). Common insecticides of these two groups includes chlorpyrifos, diazinon, carbufuran, carbosulfan and fenobucarb, has been using to control *N. lugens* field populations. However, the threat of *N. lugens* resurgence is still presence as low to high levels of resistance to chlorpyrifos has been documented (Fig. 2) (Lu et al, 2017; Yang & Lai, 2019).

Resistance to neonicotinoids

Imidacloprid a widely used neonicotinoid has become an effective solution to control many chewing and sucking pest, including *N. lugens* since 1991 (Masaya et al, 2008).

However, the continuous and overuse of the insecticide faced a challenge when reduced toxicity of imidacloprid has been reported in *N. lugens* field populations across Asian countries (Bao et al, 2016). High to extremely high levels of resistance to imidacloprid has been reported for several consecutive years in China, Japan, Vietnam, Bangladesh and Thailand (Wang et al, 2014; Bao et al, 2016; Garrood et al, 2016; Sanada-Morimura et al, 2019; Datta et al, 2021b). Other neonicotinoids such as thiamethoxam, dinotefuran, sulfoxaflor, clothianidin, cycloxaprid, and nitenpyram were effective, but in recent year's development of resistance in *N. lugens* to these insecticides also reported (Pang et al, 2014; Mu et al, 2016; Fang et al, 2018; Sun et al, 2018; Mao et al, 2019; Zhang et al, 2020). These findings suggest that reduced toxicities of several neonicotinoids have been threatened pest control measure of *N. lugens*.

Resistance to other insecticides

Resistance to insecticides belong to pyrethroids (pymetrozine, etofenprox), and insect growth regulator (buprofezin) have been found in *N. lugens* in recent years (Yang et al, 2016; Sun et al, 2017; Liao et al, 2019; Datta et al, 2021b). In contrast, a new mesoionic insecticide triflumezopyrim still shows its efficiency to control *N. lugens* (Liao et al, 2021). Although the levels of resistance to these insecticides are comparatively low than neonicotinoids, there is a threat of complete control failure in future by these insecticides. Therefore, it is important to monitor insecticide resistance development in rice insect pests regularly.

Resistance selections - method to understand resistance potentiality

Various experiments designed to find out how quick insecticide resistance could increase or reduce in an insect pest in response to a single or multiple insecticides and what are the responses of the pest against different insecticides after certain generations of rearing in laboratory condition (Jin et al, 2019; Liao et al, 2019). For these objectives, researchers, rear the pest with insecticides termed as resistance selection. This method helps to understand the potentiality of resistance development in *N. lugens*, to advance molecular study to gather more knowledge on resistance mechanisms, and suggests rational use of insecticides. Susceptible *N. lugens* developed low to high levels of resistances to imidacloprid, etofenprox and clothianidin when resistance selection was done with the same insecticide for several generations (Zhang et al, 2015; Sun et al, 2017; Jin et al, 2019). Resistance selection method helps to get a highly resistant strain to a single insecticide that make it possible to conclude the contribution of a sole resistance mechanism in developing resistance.

CONCLUSIONS

In last decades side by side the resurgence of *N. lugens,* use of insecticides has also been significantly increased. This major rice pest already developed low to high levels of resistances to commonly used insecticides in most of the rice producing Asian countries. Increased detoxifying enzyme activities have been found as the principal resistance mechanism in *N. lugens.* Enhanced activities of P450, EST, and

GST have been significantly contributes in evolution of resistance to neonicotinoids, pyrethroids, insect growth regulator and to organophosphate insecticides. Thus it shows that this pest have the potentiality to develop resistance to multiple insecticides in field condition. Hence, many studies have been carried out to understand particular molecular mechanisms presence in *N. lugens.* To delay or abandoned the resistance development in this pest, rotational use of insecticides, introducing new class of insecticides, understanding multi-resistance mechanism and adapting the insecticide resistance management strategies are recommended.

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Received: February 16, 2021 *Accepted: August 27, 2021*