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# Glycosyltransferases: the multifaceted enzymatic regulator in insects

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## Abstract

**Glycosyltransferases (GTs) catalyse the reaction of glyco-conjugation of various biomolecules by transferring the saccharide moieties from an activated nucleotide sugar to nucleophilic glycosyl acceptor. In insects, GTs show diverse temporal and site-specific expression patterns and thus play significant roles in forming the complex biomolecular structures that are necessary for insect survival, growth and development. Several insects exhibit GT-mediated detoxification as a key defence strategy against plant allelochemicals and xenobiotic compounds, as well as a mechanism for pesticide cross-resistance. Also, these enzymes act as crucial effectors and modulators in various developmental processes of insects such as eye development, UV shielding, cuticle formation, epithelial development and other specialized functions. Furthermore, many of the known insect GTs have been shown to play a fundamental role in other physiological processes like body pigmentation, cuticular tanning, chemosensation and stress response. This review provides a detailed overview of the multifaceted functionality of insect GTs and summarizes numerous case studies associated with it.**

**Keywords: Allelochemicals, development, detoxification, glycosyltransferases (GTs), insects.**

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## Introduction

Food availability can be governed by intrinsic factor-like exposure to dietary toxins, and anthropogenic toxins including insecticides. Challenges with these allelochemicals (plant toxins) can play important roles in the modulation of insect metabolic systems. These metabolic systems are composed of a variety of modifying enzymes like, Glycosyltransferases (GTs), Cytochrome P450s (CYP), esterases and other related enzymes that help insects to detoxify plant allelochemicals, xenobiotic compounds and pesticides (Li *et al*., 2018). As a molecular function, Glycosyltransferases (GTs) family of enzymes adds sugar groups to lipids, proteins and nucleic acids. The addition of sugar groups by GTs to these biomolecules can alter their activity and functionality (Liang *et al*., 2015). GTs are classified based on several nucleotide sugar donors such as uridine diphosphate (UDP), guanosine diphosphate (GDP) and cytidine monophosphate (CMP). GTs transfer the sugar moiety from an activated nucleotide donor (e.g., UDP-Gal, GDP-Man, CMP-NeuAc) or a lipid phospho-sugar (e.g., dolichol phosphate) to the nucleophilic oxygen or nitrogen of the acceptor molecule (Lairson *et al*., 2008). In prokaryotes, glycosylation reactions occur in the cytoplasm and periplasmic space, whereas in eukaryotes, glycosylation takes place in the cytosol, Golgi complex and endoplasmic reticulum (Liang *et al*., 2015). In insects, GTs are involved in biological processes related to survival, growth and homeostasis by regulating diverse metabolic and physiological events such as embryo development, tissue differentiation, detoxification, chemo-sensation, endobiotic modulation and many more (Fig. 1) (Luque and O'Reilly, 2002; Nakamura *et al*., 2002; Real *et al*., 1991). Over time insects have evolved an array of physiological modulation that allows them to feed on plants by ingesting the allelochemicals, followed by their

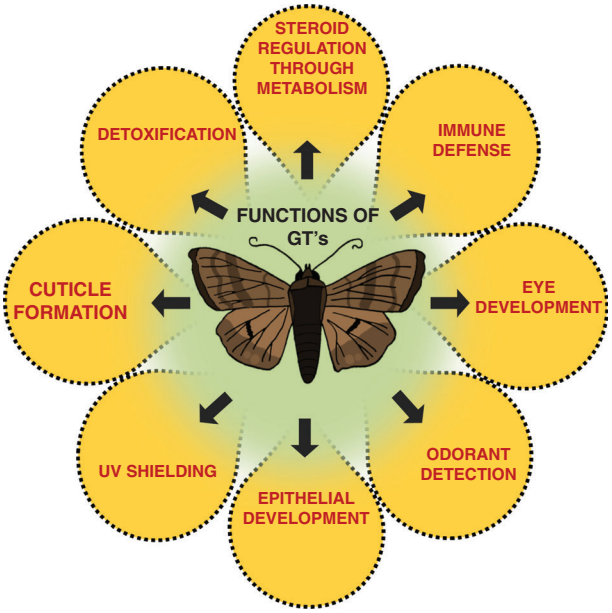


**Figure 1.** Overview of the multifaceted role of GTs in various physiological processes of insects [Colour figure can be viewed at wileyonlinelibrary.com].

rapid excretion and/or detoxification (Sorensen and Dearing, 2006; Winde and Wittstock, 2011; Opitz and Müller, 2009). Glyco-conjugation of lipophilic molecules by GTs convert them into water-soluble products, which can be readily excreted out of the insect body (Fig. 2) (Bock, 2016). Based on sequence and structural similarities, identified GTs are classified into 105 families as per the CAZy database (Cantarel *et al*., 2009; Coutinho *et al*., 2003) (Table 1). Likewise other GT candidates, most of the reported insect GTs shows differential temporal (life stage-specific), spatial (tissue-specific) or sex-specific expression patterns (Fig. 3; Table 2) (Ahn *et al*., 2012; Zhang *et al*., 2017). GTs are expressed in multiple sites throughout the insect body including the fat bodies, haemolymph, antennae, midgut, legs, wings and gonads (Bozzolan *et al*., 2014). There are few conserved UDP Glycosyltransferases (UGTs), like UGT50A1, that are expressed throughout the body in most insect species and also have orthologs in humans (UGT8A1) or other higher eukaryotes. It is thought that highly conserved and ubiquitously expressed UGTs might be involved in glycosylation of cell membrane lipid moieties and play important roles in cellular homeostasis (Ahn *et al*., 2012; Bock, 2003). In this review, we discuss and summarize the current literature describing the diverse functions of insect GTs in detoxification, development and defence.

## The indispensability of insect GTs for detoxification

Over the span of 400 million years, co-evolution between plants and phytophagous insects has led to the development of diverse mechanisms within the insects to cope with

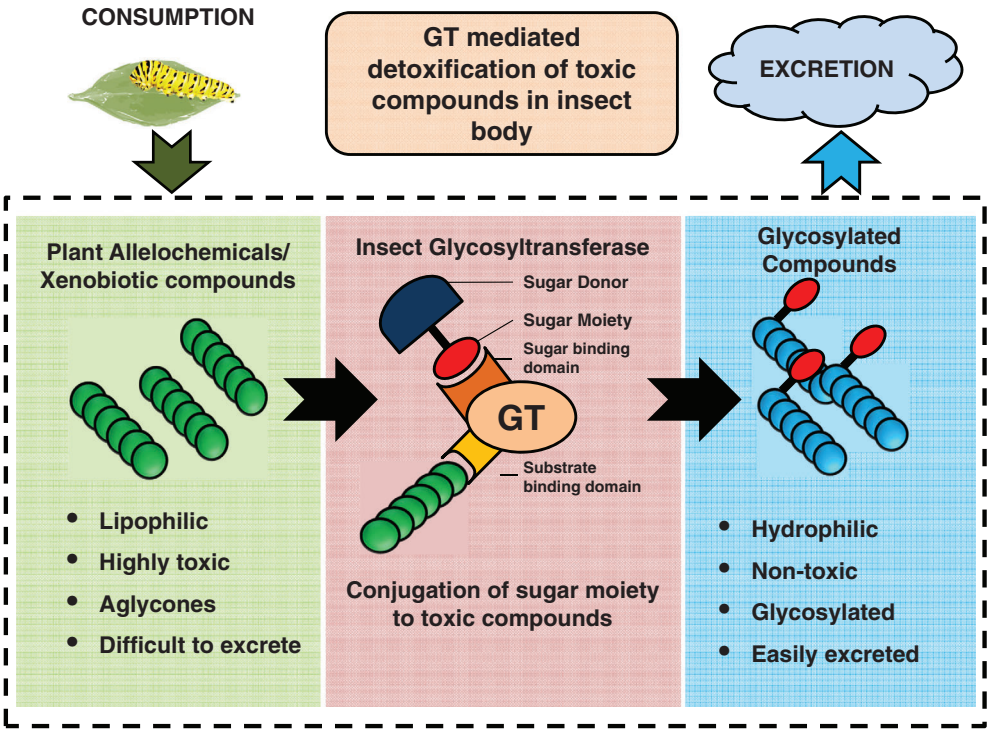


**Figure 2.** Pictorial representation of the general mechanism of GTs mediated detoxification of plant allelochemicals or xenobiotic compounds observed in insects [Colour figure can be viewed at wileyonlinelibrary.com].

**Table 1.** Number of GTs identified in various insect species and their CAZy families

| Sr. no | Insect name | Order | GT family | GT name | NO. of GTs |
|---|---|---|---|---|---|
| 1 | *Triboliumcastaneum* | Coleoptera | GT2 | chitin synthase | 4 |
| | | | GT76 | gustatory receptor candidate 30 | 1 |
| 2 | *Anopheles gambiae* | Diptera | GT2 | chitin synthase (fragment) | 1 |
| | | | GT10 | α-1,3-fucosyltransferase (AgFucTC;AgaPAGAP000365); core α-1,3-fucosyltransferase (AgTucTA;AgaP_AGAP003191) | 1 |
| | | | GT16 | ORF (fragment) | 1 |
| | | | GT23 | core α-1,6-fucosyltransferase (AgFucT6;AgaPAGAP001888) | 1 |
| | | | GT29 | α-2,6-sialyltransferase (ST6Gal) | 1 |
| | | | GT35 | glycogen phosphorylase (AgGp) | 1 |
| | | | GT61 | glycosyltransferase, partial (GlyT) (fragment) | 1 |
| | | | GT65 | protein *O*-fucosyltransferase 1 (pofut1) | 1 |
| | | | GT68 | protein *O*-fucosyltransferase 2 (pofut2) (fragment); ENSANGG00000014992 | 1 |
| | | | GT76 | ENSANGG00000007308 | 1 |
| | | | GT90 | AgaP_AGAP008037; AgaP_AGAP004267 | 1 |
| | | | GT92 | AgaP_AGAP007718 | 1 |
| 3 | *Drosophilamelanogaster* | Diptera | GT1 | CG30438;CG4302; CG15661; CG4414; CG18869; CG3797; CG6633; CG6658; CG4739; CG17200; CG5724; CG5999; CG6475; CG10170; CG10168; CG15569; CG2788; CG11289; CG13270; CG13271; CG10178; CG17324; CG17323; CG17322 | 1 |
| | | | | CG6308 & CG14512 | 1 |
| | | | | UGT | 10 |
| | | | GT3 | CG6904 | |
| | | | GT7 | *β*-1,4-*N*-acetylgalactosaminyltransferase A; xylosylprotein *β*-4-galactosyltransferase I/7; *β*-1,4-*N*-acetylgalactosaminyltransferase B; CG12913; CG9220 | 1 |
| | | | GT8 | CG11388; CG44244; CG9996 | 1 |
| | | | GT10 | α-1,3-fucosyltransferase | 4 |
| | | | | CG9169 | 1 |
| | | | GT13 | *β*-1,2-GlcNAc transferase I | 1 |
| | | | GT14 | peptide *O*-*β*-xylosyltransferase | 1 |
| | | | GT16 | *β*-1,2-*N*-acetylglucosaminyltransferase II | 1 |
| | | | GT17 | CG31849 | 1 |
| | | | GT20 | trehalose-6-phosphate synthase | 1 |
| | | | GT21 | UDP-Glc: ceramide *β*-glucosyltransferase | 1 |
| | | | GT22 | CG3419; CG12006; CG8412; CG11851 | 1 |
| | | | GT23 | core α-1,6-fucosyltransferase | 1 |
| | | | GT24 | UDP-glucose glycoprotein α-glucosyltransferase | 1 |
| | | | GT25 | CG31915 | 1 |
| | | | GT27 | polypeptide *N*-acetylgalactosaminyltransferase | 9 |
| | | | | CG7579; CG7304; CG10000; CG31776; CG30463 | 1 |
| | | | GT29 | α-2,6-sialyltransferase (CG4871) ST6Gal I | 1 |
| | | | GT31 | CG18558; CG4351; CG8673; CG9109; CG30037; CG30036; CG34057; CG34452; CG3038; CG34056; CG11357; CG2983; CG2975; CG3119; CG8668; CG9520; CG8976; CG8708; CG7440; CG9220; UDP-GlcNAc: *O*-fucosylpeptide *β*-1,3-*N*-acetylglucosaminyltransferase/fringe (Fng; CG10580); UDP-Gal: glycosaminoglycan *β*-1,3-galactosyltransferase (Dbeta3galtII;CG8734; Dmel_CG8734); *β*-1,3-GlcNAc transferase (Brn;brainiac; CG4934) | 1 |
| | | | GT32 | UDP-GalNAc:α-1,4-*N*-acetylgalactosaminyltransferase (α-4GT1;Dmel_CG17223); CG5878 (Alpha4GT2) | 1 |
| | | | GT33 | CG18012 | 1 |
| | | | GT35 | glycogen phosphorylase (GlyP;GLYP;CG7254;Dmel_CG7254) | 1 |
| | | | GT39 | Dol-P-Man: protein mannosyltransferase (POMT2); Dolichyl-phosphate-mannose protein mannosyltransferase (POMT1) | 1 |
| | | | GT41 | UDP-GlcNAc: pepetide *O*-*β*-*N*-acetylglucosaminyltransferase (OGT;DmOGT;CG10392) | 1 |
| | | | GT43 | *β*-glucuronyltransferase-P (CG6207;IP16131); *β*-glucuronyltransferase-S (CG3881); glucuronosyltransferase-*S*-II (Glcat-S); glucuronosyltransferase-*S*-I (Glcat-S) (fragment) | 1 |
| | | | GT47 | CG8433 (Dext2;sotv); tout-velu (CG10117;Dext1;ttv); heparan sulfate α-1,4-*N*-acetylglucosaminyltransferase-I/II (CG15110;Dext3;botv) | 1 |
| | | | GT49 | RE56074p (CG11149); CG15483; CG9171; CG3253 | 1 |

(*Continued*)

**Table 1.** Continued

| Sr. no | Insect name | Order | GT family | GT name | NO. of GTs |
|---|---|---|---|---|---|
| | | | GT50 | CG9865 | 1 |
| | | | GT54 | CG9384; CG17173 | 1 |
| | | | GT57 | CG5091 (LD29083); CG4542 (Xit;Xiantuan) | 1 |
| | | | GT58 | CG4084 | 1 |
| | | | GT59 | Alg10 (CG32076) | 1 |
| | | | GT61 | [protein] EGF20 *O*-$\beta$-*N*-acetylglucosaminyltransferase (Eogt; EOGT; CG9867) | 1 |
| | | | GT64 | CG8433 (Dext2; sotv); tout-velu (CG10117; Dext1; ttv); heparan sulfate $\alpha$-1,4-*N*-acetylglucosaminyltransferase-I/II (CG15110; Dext3; botv) | 1 |
| | | | GT65 | GDP-L-Fuc: protein *O*-$\alpha$-L-fucosyltransferase (CG12366-PA; *O*-fut1; Ofut1; Nti; FI01906p) | 1 |
| | | | GT66 | CG1518-PA; CG7748-PA (OstStt3) | 1 |
| | | | GT68 | TSR-specific *O*-fucosyltransferase (CG14789; GH07929p) | 1 |
| | | | GT76 | CG6657 (Veg) | 1 |
| | | | GT90 | UDP-Glc: protein *O*-$\beta$-glucosyltransferase/UDP-Xyl: protein *O*-$\beta$-xylosyltransferase (RumI;Poglut;Poglut1;CG31152-PA; Dmel_CG31152); Dmel_CG31139 | 1 |
| | | | GT92 | Dmel_CG12910; Dmel_CG3655; Dmel_CG9395; Dmel_CG12715 | 1 |
| | | | GT105 | CG4050; CG5038; CG4341; CG31690 | 1 |
| 4 | *Acyrthosiphonpisum* | Homoptera | GT1 | ACYPI001237 | 1 |
| | | | GT68 | ACYPI004711 | 1 |
| 5 | *Apismellifera* | Hymenoptera | GT10 | $\alpha$-1,3-fucosyltransferase A; $\alpha$-1,3-fucosyltransferase B; $\alpha$-1,3-fucosyltransferase C | 1 |
| | | | GT24 | UDP-Glc: glycoprotein glucosyltransferase (UGT;GB16829) | 1 |
| | | | GT31 | $\beta$-1,3-galactosyltransferase | 4 |
| 6 | *Aphis gossypii* | Hemiptera | GT1 | UDP-glucuronosyl transferase | 31 |
| 7 | *Bombyxmori* | Lepidoptera | GT2 | Glycosyltransferase | 1 |
| | | | | Chitin synthase | 2 |
| | | | GT7 | Glycosyltransferase | 1 |
| | | | GT10 | core alpha 1,3-fucosyltransferase | 1 |
| | | | GT13 | Acetylglucosaminyltransferase | 1 |
| | | | GT23 | $\alpha$-1,6-fucosyltransferase | 1 |
| | | | GT25 | Bm6922 | 1 |
| | | | GT27 | *N*-acetylgalactosaminyltransferase | 1 |
| | | | GT31 | Fringe (Fng) | 1 |
| | | | | Glycosyltransferase | 2 |
| | | | GT35 | Glycogen phosphorylase | 1 |
| | | | GT43 | Glucuronyltransferase | 1 |
| | | | GT65 | Protein-*O*-fucosyltransferase 1 (Fut12) (fragment) | 1 |
| | | | GT68 | Protein-*O*-fucosyltransferase 2 | 1 |
| 8 | *Helicoverpaarmigera* | Lepidoptera | GT2 | $\beta$-1,4-mannosyltransferase | 1 |
| | | | | Chitin synthase | 5 |
| | | | GT7 | beta 1,4-*N*-acetylgalactosaminyltransferase | 1 |
| | | | GT20 | trehalose 6-phosphate synthase | 2 |
| | | | GT31 | $\beta$-1,3-glycosyltransferase | 2 |
| 9 | *Manducasexta* | Lepidoptera | GT2 | Chitin synthase | 2 |
| 10 | *Plutellaxylostella* | Lepidoptera | GT2 | glycosphingolipid synthetase (Bre-3) | 1 |
| | | | | chitin synthase 1 | 3 |
| | | | | $\beta$-1,4-mannosyltransferase (Bre3) | 1 |
| | | | GT7 | $\beta$-1,4-mannosyltransferase (Bre3); $\beta$-1,4-*N*-acetylglucosaminyltransferase (Bre4) | 1 |
| | | | GT31 | Glycosphingolipid synthetase (Bre-5); $\beta$-1,3-*N*-acetylglucosaminyltransferase (Bre5) | 1 |
| 11 | *Zygaenafilipendulae* | Lepidoptera | GT1 | UDP-glycosyltransferase | 11 |
| 12 | *Tetranychusurticae* | Trombidiformes | GT1 | UDP-glycosyltransferase | 79 |
| | | | GT2 | Chitin synthase | 7 |

a diversity of plant chemical defences (Després *et al*., 2007). Most insect species use multiple mechanisms that include ingestion avoidance, excretion, sequestration and detoxification to overcome detrimental effects of allelochemicals such as alkaloids, terpenes and phenols (Heidel-Fischer and Vogel, 2015; Krempl *et al*., 2016; Rane *et al*., 2016). Herbivorous insects are often exposed to toxic plant compounds upon feeding, and thus many insects possess proficient resistance mechanisms like detoxification machinery (Ramsey *et al*., 2010). Glyco-conjugation of toxic compounds by GTs and their subsequent excretion is a prime route, among the detoxification processes (Fig. 2). Glyco-conjugation of allele-chemicals helps in the compartmentalized storage to increase their solubility and to reduce

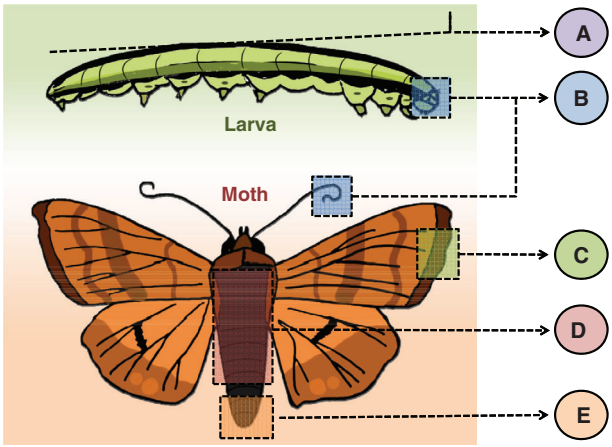


**Figure 3.** Differential tissue-specific localization of GTs and their representative functions. (A) GTs involved in development-related functions are expressed in haemolymph cells and in the overall insect body; (B) Antennal GTs play important role in chemosensation related functions such as detoxification of sex pheromones; (C) GTs present in wings are involved in cuticle development; (D) GTs in gut participates in detoxification and metabolism of ingested xenobiotics and allelochemicals; (E) GTs expressed in lower abdomen and legs function in detoxification of allelochemicals from oviposition sites. [Colour figure can be viewed at wileyonlinelibrary.com].

their autotoxicity (Kannangara *et al*., 2018). Along with GTs, many other families of enzymes can be involved in detoxification, such as glutathione-*S*-transferases (GST), phosphotransferases, sulfotransferases, aminotransferases and glycosidases (Berenbaum and Johnson, 2015). Many of these enzyme families are proved to be an outcome of Horizontal Gene Transfer (HGT) between prokaryotic organisms and arthropod genome (Wybouw *et al*., 2016). For example, the phylogenetic reconstruction and sequence similarity between bacterial UGTs and *Tetranychus urticae* UGTs suggest that this insect has acquired these UGTs from bacteria by HGT (Ahn *et al*., 2014; Wybouw *et al*., 2018). Also, the previous study has shown the functionally active expression of these UGTs in bacterial system proving their prokaryotic origin during chelicerate evolution (Snoeck *et al*., 2019).

### *GT-mediated detoxification of plant allelochemicals*

Several reports have highlighted the roles and mechanisms of the GT-mediated detoxification process with respect to plant allelochemicals (Ahn *et al*., 2011b; Heidel-Fischer and Vogel, 2015; Krempl *et al*., 2016) (Table 1). In *Myzus persicae* nicotianae, it is suggested that four highly expressed UGT genes of UGT330A3, UGT344D5, UGT348A3 and UGT349A3 could be required in the detoxification of nicotine or its primary metabolites, as RNAi-mediated silencing of these genes reduced the tolerance towards nicotine (Pan *et al*., 2019). Similarly, One of the best-known GT-mediated processes is the detoxification of Capsaicin. Capsaicin is a plant metabolite expressed in various Capsicum pepper species. Capsaicin is recognized as a potential feeding deterrent, oviposition inhibitor and is also responsible for larvicidal activity in several insects (Cowles *et al*., 1989; Hori *et al*., 2011; Madhumathy *et al*., 2007; Weissenberg *et al*., 1986). However, some lepidopteran insects like *Helicoverpa armigera*, *Helicoverpa zea* and *Helicoverpa assulta* have developed the ability to detoxify capsaicin by glycosylation with the help of GTs, after which they excrete the inactivated toxin in the form of capsaicin glucoside (Ahn *et al*., 2011b).

Similarly, in other lepidopteran insects like *Spodoptera frugiperda*, GT-mediated detoxification is utilized to detoxify maize plant indole-derived defensive compounds, specifically benzoxazinoid (BXD). BXD gets converted into an active aglucone form by the action of ß-glucosidases in the insect gut. The detrimental effect of this aglucone on growth and survival of several Lepidopteran species has been documented, for example, aglucones can delay the growth and decrease the survival rates in several Lepidopteran species (Krempl *et al*., 2016; Wouters *et al*., 2014). As a counter mechanism, *S. frugiperda* re-glycosylates the aglucone in an inverted topology converting it back to its inactive form. Inverted glycosylation avoids the reactivation of the substrate by insect gut ß-glucosidases. Hence, in this way, the insects can dodge the activity of the aglucones through its stereochemical inversion to stabilize and deactivate the plant defensive compound (Maag *et al*., 2014; Wouters *et al*., 2014). Additionally, a comparison between *Spodoptera littoralis* and two *Spodoptera frugiperda* strains (Corn and Rice) showed that the total expression of UGT-encoding genes did not change between larvae feeding on artificial diet and on maize leaves. This finding suggests that the that UGT responsible for BXD glucosylation is constitutively expressed in both the *Spodoptera* species, rather than being induced upon contact with BXDs (Roy *et al*., 2016).

Gossypol is a natural defensive compound of cotton plants. The hydrophobic nature of this compound allows it to diffuse across the membrane and thus harm the insects that ingest the cotton plants (Laughton *et al*., 1989). Glycosylation of gossypol, into less-toxic diglycosylated gossypol isomer 4 and 5 by the action of GTs could be a vital survival tactic of *H. armigera* and *Helicoverpa virescens* against toxic metabolites from host plant e.g. gossypol in cotton (Krempl *et al*., 2016). Interestingly, *H. armigera* shows a differential reactivity and substrate selectivity, thus it produces a higher amount of the diglycosylated gossypol isomers 4 and 5 as compared to contemporary *H. virescens*. The differences in the preferences for isomer formation between related species might be attributed to the differences in the regioselectivity of UGT41B3 and UGT40D1, which are responsible for glycosylation of

**Table 2.** The location and function of different GTs in selective insects

| GTs name | CAZy family | Organism | Tissue | Function | Reference |
|---|---|---|---|---|---|
| *Detoxification* | | | | | |
| Dorothy | GT1 | *Drosophila melanogaster* | Lymph gland, Hemocytes, pericardial cells | Detoxification of xenobiotics | Zhou *et al*. (2011) |
| BmUGT-013829 | GT1 | *Bombyxmori* | Larval head, Antenna, Midgut, Integument | Olfaction, flavonoid detoxification | Huang *et al*. (2008) |
| Capsaicin UGT | - | *Helicoverpaarmigera* | Fatbody, midgut | Capsaicin metabolism | Ahn *et al*. (2011a) |
| UGT2B5 | - | *Leptinotarsadecemlineata* | Midgut, fat body, and malpighian tubules. | Imidacloprid resistance | Kaplanoglu *et al*. (2017) |
| UGT33A1 | GT1 | *Zygaenafilipendulae* | Haemocytes, malphigian tubules, fatbody and integument | Cyanogenic glucosides metabolism | Jensen *et al*. (2011) |
| AlUGT33AD1 | - | *Athetis lepigone* | Male antenna | degradation of sex pheromones and plant volatiles | Zhang *et al*. (2017) |
| *Embryonic development, tissue differentiation and metamorphosis* | | | | | |
| Brainiac | GT31 | *Drosophila melanogaster* | Developing CNS, retina, and adult, hippocampus | Brain and eye development | Gramates *et al*. (2017) |
| Egghead | GT2 | *Drosophila melanogaster* | Maternal effect genes during development, larval tissues | Development, Oogenesis | Goode *et al*. (1996) |
| β4GalNAcTA/B | GT7 | *Drosophila melanogaster* | Larval tissues | Synthesis of glycosphingolipids | Chen *et al*. (2007) |
| POGLUT1/RUMI | GT90 | *Drosophila melanogaster* | Larval tissues | Glycosylation of Eye Shut protein for eye development | Husain *et al*. (2006) |
| Fringe | GT31 | *Drosophila melanogaster* | Dorsal cells of larva | Extension of *O*-Glycans in Notch, Dorso-Ventral patterning, wing development | Moloney *et al*. (2000) |
| FuctA alpha1,3-fucosyltransferase A | GT10 | *Drosophila melanogaster* | Neural ectoderm | Neuronal development | Walski *et al*. (2017) |
| Drosophila UDPGlc: Glycoprotein glucosyltransferase (DUGT) | GT8 | *Drosophila melanogaster* | Embryonic tissues | Transfer of glucose to denatured proteins; discrimination between malfolded and native glycoproteins | Parker *et al*. (1995) |
| Tyrosine $\beta$-glucosyltransferase | - | *Manducasexta* | Fat body, labial gland, midgut | synthesis of the pupal cuticle tanning precursor tyrosine glucoside | Ahmad *et al*. (1996) |
| *Additional physiological processes* | | | | | |
| BmUGT-10286 | GT1 | *Bombyxmori* | Silk gland, mid gut | UV-shielding by Quercetin metabolism | Daimon *et al*. (2010) |
| Phenol β glucosyltransferase | - | *Dissosteiracarolina* | Wings | Catalyses glucosylation of the 3-OH of quercetin | Ahmad and Hopkins (1993) |
| Chitin synthase TcCHS1 | GT2 | *Triboliumcastaneum* | Midgut | Cuticle development, exoskeleton formation | Arakane *et al*. (2004) |

gossypol in these insects. This species-specific difference in extent and pattern of gossypol glycosylation (Ahn *et al*., 2011a) in the above two generalist moth species suggests the evolutionary difference in detoxification machinery to aid adaptation in the presence of allelochemicals (Krempl *et al*., 2016).

In *Bombyx mori* candidate UGTs, involved in detoxification, shows differential spatial expression profiles across developmental stages. For example, Bmugt1 and BmGT010286, *B. mori* UGTs, are involved in the detoxification process of plant allelochemicals like flavonoids, coumarins and other phenolic compounds and are expressed in most of the insect tissues, like testis, ovary, head, integument, fat body, midgut, haemocyte, malpighian tubules and silk glands (Huang *et al*., 2008; Luque and O'Reilly, 2002). Furthermore, tissue-specific expression of GTs is observed in *Athetis lepigone* moth, with AlUGT42C3 and AlUGT44A7 expressed in the gut, for degrading plant allelochemicals and detoxification of insecticides (Zhang *et al*., 2017). Similarly, a recent study on

**Table 3.** List of Xenobiotic compounds, their occurrence and the GTs involved in insects for its detoxification

| Sr. no | Xenobiotic name | Occurrence | GTs involved in detoxification | Reference |
|---|---|---|---|---|
| *Plant allelochemicals* | | | | |
| 1 | Capsaicin | *Capsicum* spp. (Solanaceae) | Capsaicin UDP-glycosyltransferase (UGT) | Ahn *et al*. (2011b) |
| 2 | Benzoxazinoids (BXDs) | Maize | UDP-glycosyltransferase (UGT) | Wouters *et al*. (2014) |
| 3 | Gossypol | Cotton | UGT41B3 and UGT40D1(UDP-glycosyltransferase) | Krempl *et al*. (2016) |
| 4 | Quercetin | Mulberry | Quercetin 5-*O*-glycosyltransferase (Q5GT) | Daimon *et al*. (2010) |
| 5 | Esculetin | Plant derived phenolic compounds (Coumarins) present in most of the plant species | Phenol-$\beta$-glycosyltransferase | Ahmad and Hopkins (1993) |
| 6 | Fraxetin | | | |
| 7 | 4-Hydroxycoumarin | | | |
| 8 | Scopoletin | | | |
| 9 | Umbelliferone | | Phenol-$\beta$-glycosyltransferase | Ahmad and Hopkins (1993) |
| 10 | Luteolin | Plant derived phenolic compounds (Flavonoids) present in most of the plant species | | |
| 11 | Naringenin | | | |
| 12 | 3-Hydroxyflavone | | | |
| *Insecticides* | | | | |
| 13 | Deltamethrin | Chemical insecticide | UGT46A6 and UGT40R3 | Bozzolan *et al*. (2014) |
| 14 | Permethrin | Chemical insecticide | UDP-glycosyltransferase (UGT) | Vontas *et al*. (2005) |

*Plutella xylostella* moth confirmed the presence of 23 UGTs in both, the insect midgut and fat body. Out of these UGTs, UGT33AA4, UGT40V1 and UGT45B1 showed higher expression, in response to exposure to insecticides, in multi-resistant *P. xylostella* population. Thus, this tissue-specific varied expression suggests the putative role of these UGTs in detoxification (Li *et al*., 2018). Hence, the spatiotemporal and tissue-specific expression of UGTs, in most of the insects supports their diverse activities and functions in detoxification.

### *Role of GTs in detoxification of xenobiotic compounds*

The machinery involved in detoxification of plant toxins can also result in cross-resistance to various pesticides. Thus, the activity of GTs in host-plant detoxification may act as a pre-adaptation that facilitates the emergence of insecticide resistance (Després *et al*., 2007) (Table 3). In the case of *P. xylostella*, a chlorantraniliprole resistant population showed upregulation of a UGT2B17 transcript compared to a susceptible population, indicating its potential role in developing resistance against this insecticide (Li *et al*., 2017; Chen *et al*., 2019a). Similarly, in the Colorado potato beetle (CPB), *Leptinotarsa decemlineata*, UGT2 was identified as a putative enzyme involved in imidacloprid resistance (Kaplanoglu *et al*., 2017). The enzyme, UGT2, is responsible for catalysing the conjugation of sugar molecules to a wide range of substrates thereby increasing the solubility of the toxic compound and facilitating its excretion from the insect body. The study also showed an elevated rate of CPB mortality on silencing the UGT2 gene, due to increased toxicity of imidacloprid (Kaplanoglu *et al*., 2017). Similarly in the house fly *Musca domestica*, Mdgt1 overexpression is suggested to result in imidacloprid resistance (Reid *et al*., 2019). Chen *et al*. reported that in imidacloprid resistant *Aphis gossypii* Glover, transcriptional and proteomic analyses reveal the significant upregulation of UGT genes especially UGT344B4 and UGT344C7 (Chen *et al*., 2019a, 2019b). Increased susceptibility to acetamiprid was seen after the administration of 5-Nitrouracil (5-NU) a UGT inhibitor in the aphids (Chen *et al*., 2019b).

Recently, several UGTs were found to be constitutively overexpressed in DDT-resistant *Drosophila melanogaster*, carbamate-resistant *Myzus persicae* and neonicotinoid-resistant *Bemisia tabaci* (Pedra *et al*., 2004). Another neonicotinoid molecule, thiomethaxam is predicted to be detoxified by UGT indicated by 2 fold increase in the transcriptional level of 13 UGT genes *UGT344J2*, *UGT348A2*, *UGT344D4*, *UGT341A4*, *UGT343B2*, *UGT342B2*, *UGT350C3*, *UGT344N2*, *UGT344A14*, *UGT344B4*, *UGT351A4*, *UGT344A11* and *UGT349A2* in the resistant cotton aphid, *Aphis gossypii* Glover (Chen *et al*., 2019a; Pan *et al*., 2019). Resistance to abamectin in *Tetranychus cinnabarinus* is mediated via UGT201D3 according to a report published by Wang et al in 2018 (Wang *et al*., 2018a). Additionally, it was also demonstrated that some UGTs can be induced by exposure to insecticides such as permethrin in *Anopheles gambiae* (Müller *et al*., 2008) and by deltamethrin in *Spodoptera littoralis* (Bozzolan *et al*., 2014). These examples clearly illustrate the crucial role of GTs in pesticide detoxification in the insect body. These reports also explain and justify the prompt development of cross-resistance in the various species of insects against broad-spectrum insecticides (Isman, 2006). Thus, GTs that play a crucial role in detoxification can be knocked down using RNAi technology to enhance the effect of the natural and artificial chemical plant defensive compounds on the insect and thus develop a novel pest control strategy. A similar previous

study on the UGTs of cotton aphid, *Aphis gossypii* Glover indicate that the suppression of UGT344B4 and UGT344C7 by RNAi increased the sensitivities of aphids to bifenthrin (pyrethroid insecticide) and sulfoxaflor (sulfoximine insecticide) in the pesticide-resistant population (Chen *et al*., 2019b). Hence, it can be understood that GTs help insects to metabolize the xenobiotic compounds and thus boost their survival possibilities even in a harsh toxic environment.

### GTs regulate embryonic development, tissue differentiation and metamorphosis in insects

Similar to the detoxification process, it has been reported that several GTs play an important role in regulating developmental processes like organogenesis, metamorphosis and gametogenesis in insects (Rübsam *et al*., 1998; Walski *et al*., 2017). For example, reduction of fucosyltransferase level, a highly expressed GT in the *D. melanogaster* brain that transfers L-fucose sugar from GDP-fucose donor to acceptor substrate, causes defects in brain morphology in these insects (Walski *et al*., 2017). Similarly, sialyltransferase in *Drosophila* is another crucial GTs, that transfer sialic acid to the *N*- or *O*-linked sugar chains of glycoprotein, required for the synthesis of glycoproteins that function as a neural cell adhesion molecule in neural development (Repnikova, 2012). Also, in *Nilaparvata lugens* UGT12 was found to be overexpressed and actively participating in the increased fecundity, oviposition period, fat body and ovarian protein contents caused due to jinggangmycin (fungicide) administration. A possible mechanism of this could be through the metabolism of developmental hormones as silencing of UGT12 reduced expression of juvenile hormone acid methyltransferase and resulted in underdeveloped ovaries (Ge *et al*., 2019). Another GT, called fringe, expressed in Golgi complex of specialized boundary cells of the dorsal-ventral compartment, was found to be a key regulator of Notch signalling activation which is important for wing formation in these insects (Moloney *et al*., 2000; Wilson, 2001). This regulation of Notch signalling is a vital process for the development of insect organs such as wings, foregut (proventriculus), egg chamber and eye (Walski *et al*., 2017). Silencing of this in *Tribolium castaneum* using RNAi suggests the putative involvement of GTs in adult eclosion and survival of Coleopteran insects (Dönitz *et al*., 2015). Yet another GTs, pgant3, catalyses the transfer of *N*-acetylgalactosamine (GalNAc) to tiggrin, an extracellular matrix protein known to bind integrin and regulates cell adhesion during wing development. *Drosophila* having a mutated pgant3 leads to the separation of two epithelial cell layers, creating a localized blister shortly after eclosion (Zhang *et al*., 2008).

Glycosylation is a crucial step for the formation of proteoglycans, where a glycosaminoglycan (GAG) chain is attached to a serine residue of a protein. Signalling pathways like Hedgehog (Hh) and Decapentaplegic (Dpp) in *Drosophila* requires proteoglycans in their receptor-ligand interactions. In *Drosophila*, the GAG chain is initiated by xylose addition by a GT called xylosyltransferase, followed with the addition of a galactose moiety by β1,4-galactosyltransferase, encoded by dβ4GalT7 gene. Knockdown of dβ4GalT7 by RNAi results in an abnormal leg and wing morphology as a result of impaired Hh and Dpp signalling in insects (Nakamura *et al*., 2002; Takemae *et al*., 2003). UDP-GlcNAc:α-3-D-mannoside-β1,2-*N*-acetylglucosaminyltransferase 1 (Mgat1) is useful for complex N Glycan synthesis. It is reported that *Drosophila* Mgat1 null mutants show many developmental defects such as brain abnormalities, decreased locomotion and reduced life span which were rescued by the neuronal expression on Mgat1 (Nishihara, 2019). Drosophila β1,3-glucuronyltransferase-P (dGlcAT-P) null mutants cause ultrastructural defects in neuromuscular junction boutons in *Drosophila melanogaster* (Itoh *et al*., 2018).

GTs are also reported to be involved in the elongation of glycosphingolipids (GSLs), amphiphilic lipid molecules embedded asymmetrically in cellular membranes that face the cell surface or the lumen of vesicles (Kolter *et al*., 2002; Hirabayashi, 2012). GSLs participate in changing the composition of lipid rafts, thus regulating receptor-ligand interactions during cell signalling (Hagen *et al*., 2009). GTs like Brainiac (brn) and Egghead (egh), are found to be very important in the formation of GSLs. The egh encodes a GDP-mannose: βGlc-β1,4-mannosyltransferase synthesizing mannosylglucosylceramide (MacCer) while brn encodes a UDP-*N*-acetylglucosamine: βMan-β1,3-*N*-acetylglucosaminyltransferase (β3GlcNActransferase) responsible for the synthesis of *N*-acetylglucosaminylmannosylglucosylceramide (GlcNAcMacCer), which forms the core structure of invertebrate GSLs (Goode *et al*., 1996; Schwientek *et al*., 2002; Wandall *et al*., 2003; Chen *et al*., 2007; Yamasaki *et al*., 2018). In addition to this, brn is also important for the zygotic process of separation of neuroblasts from epidermoblasts, which is required further for oogenesis (Goode *et al*., 1996). Mutant insects for egh and brn activities were found to be lethal at the pupal stage. Whereas insects that lack the maternal, as well as zygotic activities of these genes, have truncated GSLs. These insects die during embryonic stages and have severe defects in neural and epidermal development (Hirabayashi *et al*., 2006).

Along with neuronal and embryonic development, GTs also play a vital role in insect eye development. Egh is one of the important GTs involved in eye development in *Drosophila*. During this process, the correct targeting of photoreceptor neurons (R-cells) is necessary for optic lobe development. Mutants lacking the egh gene show disruption of R1-R6 axon targeting in the lamina, disrupting the

glial sheath at the lamina/lobula cortex boundary. Similarly, another GT involved in the eye development of an insect is *O*-glucosyltransferase Rumi/POGLUT1. Rumi regulates eye development through glucosylation of evolutionarily conserved Eye Shut (Eys) glycoprotein, which is responsible for Rhabdomere separation by opening the inter rhabdomere space (IRS) in Omatidium (insect photoreceptor cells) (Husain *et al*., 2006). Eys mutant shows defective omatida, due to lack of IRS and disturbed photoreceptor organization. Eys protein contains EGF-like motifs, which is glucosylated by Rumi for its correct folding and higher stability. Rumi specifically glucosylates only the correctly folded EGF-like motifs of Eys, suggesting that Rumi also selectively avoids the glucosylation of the misfolded target protein (Haltom *et al*., 2014).

In late development and metamorphosis of insects, interference of GTs is essential for the cuticular exoskeleton remodelling. It is regulated by a specialized GT called chitin synthase, which is expressed in tracheal cuticles and in the peritrophic matrix lining of the gut of insects (Merzendorfer, 2006). Chitin synthesis is an essential process of insect development that maintains the integrity of the procuticle, the stability of the epicuticle, maintenance of epidermal morphology and activity of enzymes involved in sclerotization and pigmentation (Moussian *et al*., 2005). Inhibition of chitin synthase results in severe developmental defects at the early and late stages of insect development. In insects like *D. melanogaster*, *A. gambiae*, and *Aedes aegypti*, chitin synthase is encoded by two homologous genes CHS-A and CHS-B that belong to two different phylogenetic classes (Arakane *et al*., 2004; Merzendorfer, 2006). In *Drosophila*, the mutant of a CHS1 homologous gene krotzkopfverkehrt (kkv), resulted in head deformation (Ostrowski *et al*., 2002). RNAi studies of CHS1 in *T. castaneum* resulted in reduced egg numbers and twisted embryos (Arakane *et al*., 2004). Furthermore, the silencing of CHS1 resulted in fatal conditions like wasp-waisted or crimpled cuticle in *Bactrocera dorsalis*, while elongated distal wing pads were observed in *Nilaparvata lugens* (Wang *et al*., 2012; Chen *et al*., 2013). In the brown citrus aphid *Toxoptera citricida*, silencing the chitin synthase gene *TCiCHS*, heavily impacted the nymph's ability to moult, resulting in death (Shang *et al*., 2016). In *B. mori*, during metamorphosis, the wing disc region transcription studies show upregulated levels of CHS-A, which is responsible for the synthesis of chitin in the wing disc. Hence, loss of CHS-A would lead to the deformation of wing morphology (Ou *et al*., 2014). Also, EGF (epidermal growth factor) domain-specific *O*-GlcNAc transferase (EOGT) is crucial for larval development because EOGT mutants show irregular trachea and cuticle defects (Sakaidani *et al*., 2011; Li *et al*., 2019). Further, the loss of EOGT disrupts the Dumpy function resulting in wing blistering suggesting it could be essential for epithelial cell-matrix interactions. In such cases, the insects cannot survive beyond the pupal stage (Müller *et al*., 2013). Phenotypes demonstration abnormalities in muscle attachment and contraction results in protein *O*-mannosyltransferases (POMT) mutated larvae via disruption of myosin production and fibre attachment. In *Drosophila* embryos, the absence of POMT1 and 2 show abnormal axonal connections of sensory neurons suggesting their role in sensory feedback. While mutants also show left-handed body torsion at the last stage during the course of embryonic development (Baker *et al*., 2018; Li *et al*., 2019). GTs also play a significant role in protecting the insects against temperature sensitivity. For instance, RUMI mutants fail to eclose at high temperatures proposing the role of *O*-glucosylation in protection against heat. The decrease in the level of protein *O*-mannosyltransferases (POMT), in insects, is linked sensitivity to elevated temperature and sterility (Leonardi *et al*., 2011). Also, *O*-GlcNAc transferase knockout mutants, using CRISPR/Cas9, leading to temperature-dependent lethality, demonstrating *O*-GlcNAc functions against heat stress (Mariappa *et al*., 2018). Lastly, *O*-fucosyltransferase1(O-fut1) knock out mutants display a temperature-sensitive neurogenic phenotype implying an important temperature-sensitive function, resulting in death of the insects before completing the larval stage (Ishio *et al*., 2015; Li *et al*., 2019).

Thus, it can be concluded from the above-mentioned examples that GTs holds a significant position of one of the main regulators for the diverse developmental processes in insects. The indispensability of GTs in insect development and survival propose them as a potential target for developing insect controlling strategy. For instance, a recent study has shown the RNAi-mediated knockdown of CHSA and B genes result in enhanced mortality of *A. aegypti* mosquitoes due to decreased chitin content and also increase the susceptibility of these insects to insecticide diflubenzuron (DFB) when used in combination with the dsRNA (Lopez *et al*., 2019). A similar study was also done on *Locusta migratoria* to study the application of RNAi as a genetic tool and pest control strategy targeting GTs involved in vital physiological functions of insects (Luo *et al*., 2013).

In addition, research on insect glycosylation gives us important insights into developmental biology as insects occupy an intermediate evolutionary niche in glycobiology between lower and higher eukaryotes (Vadaie and Jarvis, 2004). Apart from a few well-known model systems, the role of glycosylation in development in insects is yet to be discovered. Gene disruption studies using recombinant DNA technology will provide novel insights into the regulation and importance of the GTs in insects (Wagner and Pesnot, 2010).

## Additional physiological processes and specialized functions where GTs are involved

### *Pigmentation*

Apart from various developmental roles, some GTs are also involved in specialized functions like cuticular tanning and

body pigmentation. For example, *Polyommatus icarus* butterflies feed on flavonoid-rich plants like *Coronilla varia* and *Medicago sativa*, and this leads to sequestration of the dietary flavonoids as a glucose conjugate in the body with the aid of GTs, which is later used to impart colour to the wings (Wiesen *et al*., 1994). Similarly, *Manduca sexta* possesses phenol-β-GTs and tyrosine-β-GTs which are involved in cuticle melanisation and cuticle sclerotization, respectively (Ahmad and Hopkins, 1992; Ahmad *et al*., 1996). In these insects, phenol $\beta$-glucosyltransferases are expressed in the labial gland and fat bodies where they are crucial in the glycosylation of phenolic substrates found in plant tissues, cuticular tanning and pigmentation (Ahmad and Hopkins, 1992; Ahmad and Hopkins, 1993). Whereas tyrosine $\beta$-glucosyltransferase in *M. sexta* is observed to be expressed in labial glands, midgut, malpighian tubules and hindgut where it is required for the formation of *o*-diphenolics and quinonoid derivatives of tyrosine, necessary for cuticle sclerotization (Ahmad *et al*., 1996). In dipteran species like *Drosophila brusckii*, *Sarcophaga bullata* and *Musca domestica* tyrosine GTs form phenolic compounds that serve as reservoirs of tyrosine for pupal cases sclerotization (Chen *et al*., 2007). In yet another exclusive functionality of GTs quercetin 5-*O*-glycosyltransferase (Q5GT), in *B. mori*, catalyses the formation of quercetin 5-*O*-glucoside. It is a major constituent of cocoon flavonoids that emit bright yellow fluorescence under UV light. This flavonoid acts as a chemical UV shield and protects the pre-pupae from the harmful effect of UV radiation during metamorphosis (Daimon *et al*., 2010). Another GT, isolated from *Dactylopius coccus* DcUGT2 is crucial for the biosynthesis of Carminic acid, a well-known red colouring agent, used in food and pharmaceutical products as a dye and is also used as a microscopic stain (Kannangara *et al*., 2018).

### *Odorant sensing*

GTs are also observed to be participating in the metabolism of volatile signal molecules that are significant in chemosensation (Bock, 2016). Antennal GTs are likely to play a crucial role in insects for odorant detection and detoxification. Previous studies have reported the probable role of GTs in chemo-sensation by analysing the expression profiles of antennal specific GTs on exposure to pheromones and plant volatile compounds (Bozzolan *et al*., 2014). Similarly, SlUGT40R3 and SlUGT46A6 from male *S. littoralis* moths when exposed to sex pheromone or ester plant volatiles compounds showed high expression in the antennae (He *et al*., 2017). Similar studies of antennal UGTs have also been conducted in three insects species, namely, *D. melanogaster* (Wang *et al*., 1999), *B. mori* (Huang *et al*., 2008) and *M. sexta* (Robertson *et al*., 1999), suggesting the significance of GTs in olfaction. It has been reported that *A. lepigone* moth shows a sex-biased expression of multiple AlUGTs in chemosensory organs such as antennae. These UGTs are involved in specific functions in different sexes, such as the degradation of sex pheromones in males and the degradation of plant volatiles from oviposition sites in females. The study concludes that the *A. lepigone* UGTs AlUGT33AD1, AlUGT40F6 and AlUGT40L4 explicitly show a male-biased expression, while AlUGT33B18, AlUGT33F10, AlUGT40Q3 and AlUGT41D3 show female-biased expression (Zhang *et al*., 2017). Further, BmUGT013829 is reported to play a probable role in insect olfaction with high expression observed only in head and antenna region of *B. mori*, in both the larval and adult stages (Huang *et al*., 2008). Also, in a recent report, it was observed that HparUGT1265-1, HparUGT3119 and HparUGT8312 were highly expressed in antennae of beetle *Holotrichia parallela* and are more likely to function in odorant inactivation and olfaction (Wang *et al*., 2018b). Thus, GTs are believed to be playing a significant role in insect chemosensation by participating in odorant molecule deactivation and pheromone degradation. But to understand the molecular mechanism of this GT function, we still need further study exploring the direct molecular interaction of insect GTs with the odorant substrate and the enzyme kinetics involved in it.

### *Insect defence system*

In a few cases, GTs are also shown to be involved in insect defence systems against various external and internal threats such as predator attacks, physiological dysfunctions, etc. For example, in insects, *Dorothy* encodes putative UGTs in the haematopoietic system, pericardial cells and posterior signalling centre. *Dorothy* is predicted to be membrane-bound, playing a variety of roles in immune defence, steroid regulation and protection against xenobiotics (Burchell and Coughtrie, 1989). In *D. melanogaster*, a UDP-Glc: glycoprotein glucosyltransferase is reported to function as an endoplasmic reticular sensor of newly folded glycoproteins (Parker *et al*., 1995). It can differentiate between misfolded and native glycoproteins and may be useful in guiding chaperone systems to assist newly synthesized proteins in achieving their final, native form. Furthermore, Carminic acid, synthesized by DcUGT2 in *Dactylopius coccus*, is observed to deter ants from feeding on them (Kannangara *et al*., 2018). It is observed that despite their diverse roles, research featuring functional studies of insect GTs are lesser compared to genomic or transcriptomic studies. Thus, the limitation of this understanding of GTs can be resolved with robust and defined bioassays, providing a basis for the potential of GTs as a molecular tool.

In summary, insect GTs have been well explored for their critical role in detoxification, development and other specific functions. The role of GTs in insect immunity and adaptation can be studied thoroughly in the future to have better insights. *Further*, GTs in insects are specific in terms of

function and expression, and hence they could be a potential target for designing the next generation of insect control molecules. *Their indispensability in the development increases their advantage as pesticide targets (Lopez et al*., 2019*)*. Biocatalytic application of insect GTs, like plant and bacterial GTs, is a thriving area for protein engineering and green chemistry. Also, the diverse plethora of insect GTs can be utilized to increase the hydrophilic nature of a varied range of lipophilic molecules used in the cosmetic, food and drug industry (Geisler and Jarvis, 2010). Many complex synthetic oligosaccharides can be synthesized by the combined use of insect glycosidase and GTs as catalysts. Therapeutic proteins, nucleic acid-based products and glycol-engineered products require post-translational modifications like glycosylation, which can be achieved by using insect GTs (Geisler and Jarvis, 2010).

## Conclusion

This review highlights the significance and mechanism of numerous GTs involved in the physiological, developmental and metabolic processes of insects. In insects, GTs show differential spatiotemporal expression and localization pattern which could provide a glimpse into the diverse functions that this enzyme has. This review also outlines multiple previous reports exploring the significant functions of insect GTs in the detoxification of plant allelochemicals and xenobiotic compounds through the process of glyco-conjugation. GTs perform a crucial role in the developmental and physiological processes, like neuronal differentiation, chitin synthesis, ommatidia development, embryonal development, body pigmentation, cuticular tanning, chemosensation and defence mechanisms of insects. This disparity in the functionality of insect GTs, attributed to their localization, can be further explored for the wide-ranging applications. Therefore, the detailed investigation and characterization of insect GTs may provide new avenues for their potential application in various pharmacological, biomedical, agricultural and chemical industries and thus can strengthen the technological advances of current and future life. We believe, the summarized literature in this review may provide valuable insights into insect GTs and augment the overall understanding of their multifaceted functionality.

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## Conflict of interest

Authors have declared no conflict of interest.

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