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Structural Basis for Recognition of Gibberellin by its Receptor GID1 (GA-INSENSITIVE DWARF1) in Oil Palm

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ABSTRACT: Gibberellins (GAs) are plant hormones that are essential for many developmental processes in plants, including seed germination, stem elongation, leaf expansion, trichome development, pollen maturation and the induction of flowering. GA functions by inducing degradation of the plant growth repressor DELLA proteins. GID1 (GA-INSENSITIVE DWARF1) has a structural similarity towards the hormone-sensitive lipases (HSLs). DELLA proteins are negative regulators of GA-induced growth and dwarf stature of growth is deficient for GA is relieved by the recessive mutations in the genes coding for the members of DELLA family. There is little information available about GID1 proteins in oil palm. In this study, we have carried out homology modelling and structural identification of oil palm GID1, along with molecular docking studies with biologically active gibberellins. The protein structure analysis showed that the oil palm GID1 contains 5419 atoms, 5499 bonds, 238 H-bonds, 13 helices, 16 strands and 35 turns. Molecular docking studies revealed that GA_3 acts as the best ligand to bind with the GID1 protein compared to other biologically active gibberellins.

KEYWORDS: Oil palm, Gibberellins, GID1 (*GA-INSENSITIVE DWARF1*), Homology Modelling, Docking

I. INTRODUCTION

Gibberellins (GAs) are the plant hormones that play important roles in many aspects of plant growth and development, such as seed germination, stem elongation, and flower development [1]–[5]. GA Biosynthesis is regulated by developmental, hormonal and environmental stimuli [6]. More than 136 GAs have been identified from plants, fungi and bacteria [7]. The identification of most of the genes involved in the GA metabolic pathway has enhanced our understanding of GA pathways and their regulation [3]. Only a few GAs such as GA_1, GA_3, GA_4 and GA_7 function as bioactive (biologically active gibberellins) hormones and the non-bioactive gibberellins present in plants act as the precursors for the bioactive forms or deactivated metabolism [8]. Many genes encoding enzymes that catalyse GA biosynthesis and catabolism have been identified and are multifunctional [9]–[11]. Genetic manipulation of GAs metabolism can dramatically affect crop yield [12]. Dwarfism is caused by the mutations in the genes controlling the biosynthetic pathway of plant hormones GA [13]–[15].

GA functions by inducing degradation of the plant growth repressor DELLA proteins (e.g. GAI, RGA, RGL1, RGL2, and RGL3 in *Arabidopsis*, SLR1 in rice and RHT-1 in wheat). The DELLA family of proteins belong to a subfamily of the GRAS family of putative plant transcriptional regulators [16]–[21]. GA perception and transition are mediated by GA receptor GID1 (GA-INSENSITIVE DWARF1), which is a soluble protein having a structural similarity towards the hormone-sensitive lipases (HSLs) [22] The GA receptor gene encoding GID1 protein was first identified from a rice GA-insensitive dwarf mutant (*OsGID1*) in rice [23]. Consequently, using *OsGID1*, three *Arabidopsis* GID1 orthologs (*AtGID1*a, *AtGID1*b, and *AtGID1*c), with overlapping functions, were identified [24]. However, these mutants in *Arabidopsis* were unable to respond to GA and exhibited extreme dwarfs similar to the rice *gid1* mutant [25], [26]. DELLA proteins are negative regulators of GA-induced growth and dwarf stature of growth is deficient for GA is relieved by the recessive mutations in the genes coding for the members of DELLA family [27]. The DELLA proteins in *Arabidopsis* possess some unique functions and some are overlapping. Rice and barley have one DELLA gene each, *SLENDER RICE 1* (*SLR1*) and SLENDER (*SLR1*) respectively, in which mutations in either

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SLR1 exhibits a slender plant which is resistant to the effects of GA application [28]. The *gid1* mutant in rice is similar to GA deficient plants which might have knocked out the only GA receptor [29].

Oil palm (*Elaeis guineensis* Jacq.) is a diploid monocotyledon belonging to the family Arecaceae. It is an economically important source of the most traded vegetable oil in the international market, and is increasingly used in the food industry. It occupies the second rank in the world for oil and fat production. There are two important species in the genus *Elaeis*, *E. guineensis* and *E. oleifera*. This diploid monocotyledon is persistent in the dominance of the single vegetative apex, hence producing no adventitious or auxiliary shoots. The center of origin of the oil palm is the tropical rainforest region of West and Central Africa. Nowadays, role of oil palm consumption is increasing as a precursor in biodiesel production. Therefore, oil palm has become an important economic plant for industrial exploitation as an alternative energy source [30]–[32].

In the present study, we have carried out the homology modelling and structural identification of GID in oil palm to reveal the structural basis of gibberellin recognition in the palm.

II. RELATED WORK

Mechanism of GID1 and DELLA proteins signalling was studied by Uegenchi- Tanaka and colleagues in rice [23]. It has been proposed that both GID1 and hormone sensitive lipases (HSL) possess same structural homology and GID1 forms a receptor pocket that binds to GA. Thus HSL and GID1 proteins undergo conformational changes that allow interaction between the HSL-like "lid" of the GID1 receptor pocket and two of the DELLA protein domains, the signature "DELLA" domain and the THVYNP domain. GA becomes bounded within the pocket as the GID1 "lid" interacts with SLR1. After GA/GID1/DELLA complex is formed, binding to the F-box protein, SLEEPY1 (SLY1), gets enhanced which leads to the degradation of DELLAs through the 26S proteasome [33]. The DELLA degradation relieves the growth suppression caused by DELLAs and results in GA induced growth and other GA responses. Thus any deletion in the DELLA domain causes dwarf phenotypes which cannot be reversed by GA treatment [13], [19], [28], [34]–[36]. The natural mutations in DELLA domain deletions were chosen by plant breeders in order to create dwarf phenotypes as a part of green revolution in the 20th century. However, DELLA proteins with domain deletions cannot bind GID1 and are stable as they are not degraded as a part of DELLA/GID1 complex and acts as negative regulators of GA signalling. This is helpful in the case of agriculture because it will lead to the development of dwarf varieties which are high yielding and more resistant to lodging.

III. METHODOLOGY

The oil palm GID1 (XM_010940559.1) protein sequence was retrieved from NCBI website. NCBI BLAST [37] search was used to identify the template for modelling the three dimensional structure of GID1from the protein sequence. Three dimensional structure predictions were carried out by homology modelling using Modeller V 9.11 [38] and validated using Ramachandran plot using Rampage (http://mordred.bioc.cam.ac.uk/~rapper/rampage.php). Further processing of protein structure was carried out by "protein preparation wizard" Maestro (Version 10.1.012, Schrödinger, LLC, New York, NY, 2014). The minimization process was done by utilizing in-build constraint of RMSD: 0.3 Å and force field: OPLS 2005 (Optimized Potentials for Liquid Simulations-2005). The active site of stabilized GID protein was predicted by using 'SiteMap' and receptor grid was prepared by 'Receptor Grid Generation'. Structures of biologically active gibberellins (GA_1, GA_3, GA_4 and GA_7) compounds were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/). The selected ligands were prepared by 'LigPrep' module in Schrödinger modelling environment. Molecular docking studies were carried out by extra precision (XP) docking platform in 'Glide' module.

IV. RESULTS AND DISCUSSION

This is the first report on structural identification of gibberellin recognition GID1 in oil palm and its interaction with the biologically active gibberellins. Oil palm GID1 resembles the structural similarity towards the hormone-sensitive lipases (HSLs) the HSL family, which includes enzymes involved in lipid metabolism as expected

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and same was proved by many researchers [22], [23], [33], [42]. The difference between GID1 and HSL structures in the function of an amino acid terminal [22].

The DELLA subfamily proteins of the GRAS superfamily play an important role in the negative control of GA signalling. Members of the DELLA subfamily contain the conserved amino acid motifs DELLA (hence its name) and TVHYNP near their N-terminal portion [21], [39], [40]. All available evidences indicates that DELLA proteins are subject to GA-dependent proteolysis via the ubiquitin-proteasome pathway [1], [41]. DELLA proteins are highly conserved in many plants and the DELLA genes are well known for the role in the green revolution breeding program [27], [33], [42]. There are enough studies carried in *Arabidopsis* and cereals on GID as they produce dwarf phenotypes. GA-GID1 binding induces the formation of GID1–GA–DELLA and triggers GA action. However, the binding affinity depends upon the GA sensitivity and the binding preference of GID1 accordingly in different plants [22].

In the present study, we have carried out homology modelling and structural identification of GID1 and molecular docking study in which the structurally stable oil palm GID1 of 348 amino acids was docked with biologically active gibberellins GA_1, GA_3, GA_4 and GA_7. The structure obtained by homology modelling has 5419 atoms, 5499 bonds, 238 H-bonds, 13 helices, 16 strands and 35 turns (Figure 1A). The predicted structure was further validated through Ramachandran Plot. The Ramachandran plot validation of protein structure revealed that 96.0 % of the amino acid residues (332 amino acids) were present in favoured region, some of them in the allowed region 2.9 % (10 amino acids) and 1.2 % (4 amino acid) residues were in disallowed region (Figure 1B). The active site of GID was predicted by using 'SiteMap'. Among the five binding sites obtained, site 1was highly conserved with the active site of the template. Site 1 was chosen in this study as the most favourable site for docking as they exhibited good glide score. The results of the docking studies are presented in the form of G-score and number of H bonds in Table 1 and presented in Figure 3. From the docking analysis, GA_1, GA_3, GA_4 and GA_7 ligands occupy almost similar conformation with a glide score of -10.217, -10.080, -9.943, -9.935Kcal/mol respectively. The glide score for GA_3 was less compared to other ligands (glide energy of -46.943), which proves that GA_3 exhibited higher stability than the rest of the ligands with three hydrogen bonds.

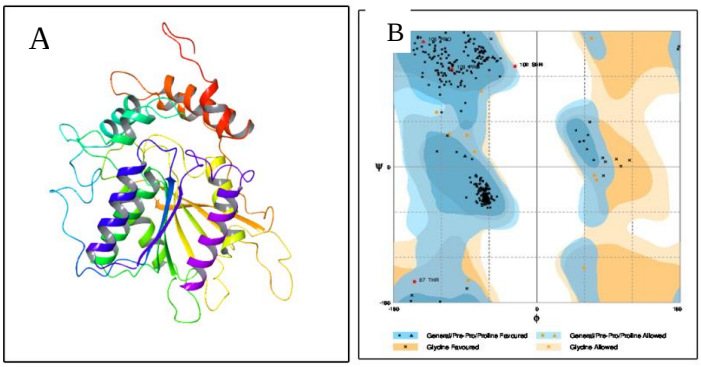

Fig. 1A. 3D structure of oil palm GID1 obtained by homology modelling with H-bonds, strands, helices and turns. Fig. 1B. Ramachandran plot analysis of modelled oil palm GID1 structure

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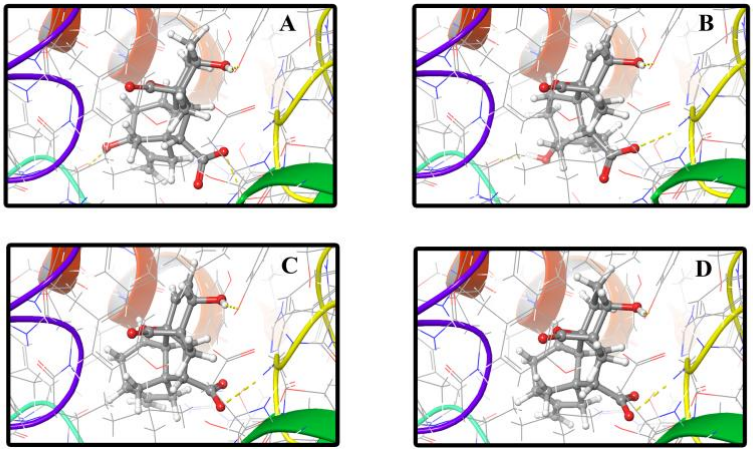

Fig. 2. Ribbon view of crystal structure of oil palm GID1 protein docked with biologically active (A) GA_1, (B) GA_3, (C) GA_4 and (4) GA_7.

Table 1. Molecular docking details of docked substrates

Protein	**Ligand**	**XP G score** (Kcal/mol)	**G Energy** (Kcal/mol)	**No. of H Bonds**
GID1	GA_1	-10.217	-45.183	3
	GA_3	-10.080	-46.943	3
	GA4	-9.943	-42.721	2
	GA7	-9.935	-43.292	2

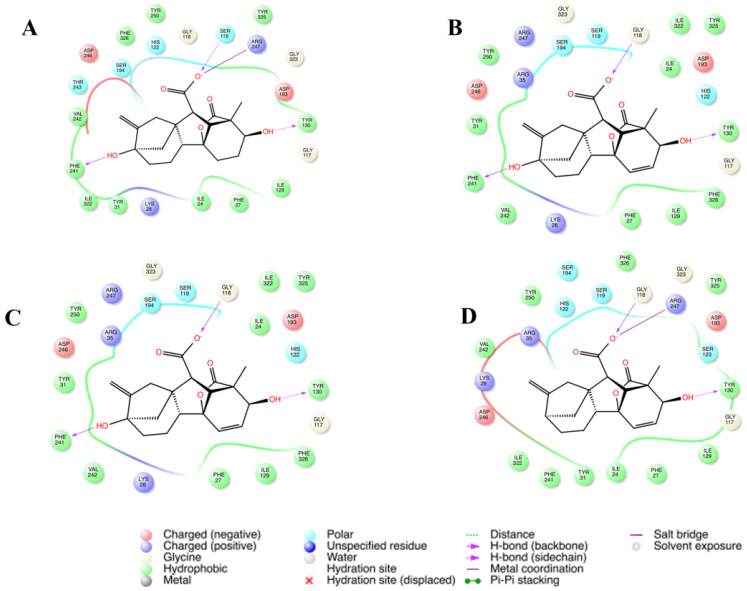

Fig. 3. GA binding activity of oil palm GID1. Binding activity of different biologically active interactions with (A) GA_1, (B) GA_3, (C) GA_4, (D) GA_7. Polar and non-polar, hydrogen interactions are shown in different colours.

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Within the GA binding pocket of oil palm GID1, the GA_1 ligand has three hydrogen bonds in which one act as the backbone and the other two are the side chains and are presented in Figure 3. The hydrogen bonds interact with hydrophobic PHE (241) and TYR (130) and also with SER (119) by polar interaction. On the other hand, GA_3 also contains three hydrogen bonds where two hydrogen bonds act as the backbone and the remaining one is the side chain. The hydrogen bonds interacts with hydrophobic PHE (241), TYR (130) and also with GLY (118). Alternatively, GA_4 and GA_7 ligands interact with GID with two hydrogen bonds, where one acts as the side chain and the other as backbones. The hydrogen bonds interact with hydrophobic TYR (130) and GLY (118) respectively. In rice, on binding of GID1 receptor by GA_4 and GA_3, SER (198) formed strong hydrogen bond with the carboxylate group at the C6 position of GA_4 [22]. However, the binding studies of oil palm GID1 showed that only GA_4 contained a SER bond interaction with the hydrogen and the other gibberellins did not show any SER interactions.

V. CONCLUSION

This study provides the structural confirmation of oil palm GID1 protein and the clear molecular interaction between the GID1 receptor and the biologically active gibberellins. The structure analysis of GID1 also would allow designing more effective gibberellins in agriculture which can be implemented for producing dwarf phenotypes. This work can be further studied using the interaction of DELLA-GID1 with *SLR* gene or making any mutations in the gene.

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