Journal of King Saud University – Science 34 (2022) 101766

Contents lists available at ScienceDirect

Journal of King Saud University – Science

journal homepage: www.sciencedirect.com

Original article

Genome wide analysis of ATP-binding Cassette (ABC) transporter in the eastern honey bee (*Apis cerana* Fabricius, 1793)

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ARTICLE INFO

Article history:
Received 1 September 2021
Revised 18 October 2021
Accepted 9 December 2021
Available online 15 December 2021

Keywords:
Docking
Exons
Gene
Honey bee
Phylogeny
Protein interaction

ABSTRACT

The ATP-binding Cassette (ABC) transporter family genes play a significant role in transporting substances such as heavy metals, phytohormones, and secondary metabolites across the structural membrane. However, it plays a vital function in the eastern honey bee (*Apis cerana*), still uncovered. The present study discovered a total of 28 ABC transporters genes in *A. cerana* genome. The ABC transporters genes phylogenetic tree gradually divide into eight groups, named from ABCA to ABCH. From these groups, ABCG belongs to the largest family containing maximum ABC transporters genes. The domain architecture and number of exon-intron differed from one gene to another gene. The exons ranged from 4 to 30. The sequence motif and alignment analysis established similar structural, functional sites in all *A. cerana* ABC transporter. In the present study results, 1st motif was observed in all genes except *XM_028666551.1*. It was observed that the *A. cerana* genes sequence illustrated synteny with *A.* dorsata. Furthermore, the biochemical and physical properties, conserved motifs, 3D (three-dimensional) structure prediction, and molecular docking with ATP molecules were also studied. Consequently, the results provided applicable information for a more functional analysis of ABC transporter genes in the honey bee and a reference study for other insects.

1. Introduction

The highly populated environment is the habitat of honey bees, where they have a strong association and food sharing with their nest-mates (DeGrandi-Hoffman and Chen, 2015). This close association causes widespread pathogens inside the bee colony. Hence, honey bees are at more risk of pathogens. This led researchers to focus on how bees maintain their health and resist the disease. Therefore, the honey bees have followed two strategies for protection against pathogens, such as innate immunity (Danihlík et al., 2015) and social immunity (Goode et al., 2006). In the first strategy, honey bees protect themselves and their colony through innate immunity; for example, the worker bees are the main pollinators, forage on crops and wildflowers. Despite this, foraging caused large exposure of honey bees with harmful pathogens (bacteria /viruses) infection and agricultural pesticides, transmitted from workers to colony bees (Raymann and Moran, 2018). In addition, the honey bees' innate immunity studies have revealed the younger forager bees have a strong innate immune system than the older foragers (Bull et al., 2012). In the second strategy, the bees' social immunity studies have revealed the health maintenance function. Worker bees smell the infected and diseased adults and broods, dumped their hive from foreign invaders/dead bodies and clear their bodies (Goode et al., 2006). Six morphologically different *A. cerana* subspecies are endemic in Asia spread throughout the Asian climatic zone series, and further used for commercial beekeeping and pollination for thousands of years. Due to morphological and behavioral similarities, *A. mellifera* and *A. cerana* are close relatives. Despite this, *A. cerana* contained various distinct features in comparison with *A. mellifera*. Such as *A. cerana* workers fanned their hives with pointing heads outward, as opposed to *A. mellifera* workers bees which ventilated with pointing heads inward; *A. cerana* foragers are good to accumulate nectars from

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jksus.2021.101766

dispersed flower resources, while in *A. mellifera* foragers, this character is neglected; *A. mellifera* used propolis (resinous material) to seal hive apertures and protect against pathogens. Furthermore, *A. cerana* is an indigenous Asian species that evolved serial striking biological features to conflict with the unfavorable conditions in their habitats. *A. cerana* foragers under cloudy situation at 7 °C temperature visit many floral species, while *A. mellifera* goes into a stagnant state at this temperature. In addition, *A. cerana* also formed a special defense mechanism set to control pathogens, parasites, and predators (Evans and Spivak, 2010).

On comparison further revealed that *A. cerana* has a hasty, unpredictable, and rapid zigzagging flight that helps to escape from bee-eating and honey birds, while *A. mellifera* has clumsy and steady flight. *A. cerana* species is an indigenous host to ectoparasitic mite (*Varroa destructor*) (Anderson and Trueman, 2000), the most injurious *A. mellifera* pest, and evolved resistance against pest across a long duration of mutual association significantly. Their worker bees can effectively eradicate mite brood and adults through successive cleaning behavior (Guan_Huang, 2005).

The ABC (ATP-binding cassette) transporters comprise the most significant superfamily protein, present in all organisms (Dean et al., 2001). These transporter proteins share extremely conserved nucleotide-binding domains (NBDs), which consist of signature motifs (the C loop), connecting two walker boxes, Walker A and Walker B (Walker et al., 1982). Additionally, to nucleotide-binding domains (NBDs), the eukaryotic ATP-binding cassette transporter usually contains one/two TMDs (transmembrane domains), comprising six to 11 membrane-spanning alpha-helices and prescribe the substrate specificity. A classic architecture domain of the whole transporter has represented the TMD-NBD-TMD-NBD sequence from N to C terminus; while half transporter contains just one NBD-TMD set. Based on NBDs homology, human transporter proteins ABC have been grouped into seven different sub-families, ABCA-ABCG. The ABCH transporter was firstly identified in *Drosophila melanogaster*, also present in Zebrafish and arthropods but absent in fungi, plants, and mammals (Tian et al., 2017).

Mainly, the transporter ABC translates membrane-bound proteins that hold many molecules, including sugar, lipids, amino acids, vitamins, peptides, sterols, endogenous metabolites, xenobiotics, hormones, and inorganics across the membrane (Dean et al., 2001). Further, these used energies are released with ATP hydrolysis during NBDs molecular transportation across the plasma membrane. It also performed a function in translation, ribosome assembly, and cell signaling (Sturm et al., 2009). Such as ABCE – ABCF transporter proteins do not work as a transporter but are involved in ribosome assembly, transcription, and translation (Tyzack et al., 2000). Moreover, the ABC transporters in plants are also involved in detoxification, phytoalexin function, and osmolality (Verrier et al., 2008).

Till now, very little is known about the ABC transporter in the *A. cerana* genome. So, the current study involved a genome-wide screening of ABC transporter in *A. cerana* genome. In addition, several bioinformatics analyses were also carried out to explore the basic and advanced features of ABC transporter; including, gene structure, phylogenetic relations, and conserved protein domains. The outcomes of this study will provide the base for further functional analysis of the ABC transporter in *A. cerana* and can also contribute to a better understanding of their molecular mechanisms.

2. Material and methods

2.1. Identification of the ABC transporters

The *A. cerana* genome was downloaded from the Honey bee genome database (https://hymenoptera.elsiklab.missouri.edu/). *Drosophila melanogaster* ABC transporter proteins were used as the query sequence. A local BLASTp similarity search was carried out to find the ABC transporters in the *A. cerana* genome. Most closely related *A. cerana* sequences were retrieved and subjected to PfamScan and Batch CDD-NCBI search to validate the presence of ABC transporters conserved domain. The data redundancy was removed, and the identified proteins sequences were used for further downstream analysis, including molecular weight (MW) and isoelectric point (IP), using ProtParam online tool, available at the ExPASy web server.

2.2. Comparative synteny analysis

To study the visualization of the genome's conservation, a synteny relative analysis was performed by the Circoletto Tool (tools.bat.infspire.org/circoletto/).

2.3. Multiple sequence alignment and phylogenetic analysis

All identified protein sequences were aligned using MUSCLE with 16 iterations. The whole transporter sequence was aligned through ClustalW and extorted to phylogenetic approach analysis with MEGA5 through 1000 replication bootstrap.

2.4. Identification of gene structure and conserved motif analysis

The intron-exon distribution was demonstrated by the gene structure display server. The ABC transporter's protein conserved motifs were determined through an online MEME server (http://meme-suite.org/) through subsequent parameters, such as no. of motifs: 20 and optimum width range: 6-200. TBtools software (http://github.com/CJ-Chen/TBtools) was utilized to build the distribution of the motifs.

2.5. Protein-protein interaction analysis

To construct the network of protein-protein interaction, the STRING 11.0 (https://string-db.org/) server was used with *A. mellifera* as the reference genome. The display parameters were set as confidence; 0.9, network; edges evidence, and maximum interaction; 10 interactions. The clustering was carried by MCL cluster with 10 inflations.

2.6. Molecular docking analysis

To find active sites, docking pockets, and comparing different ABC-transporter proteins with ATP molecules, we selected one protein from each group like ABCC, ABCG, and ABCB. Furthermore, the selected genes were ABCC5 (XM_017055838.2), ABCG4 (XM_017063007.2) and ABCB7 (XM_028668368.1). Molecular docking was done using AutoDock Vina and its associated tools. The structure of protein PDB was constructed by eliminating water molecules and heteroatoms while optimizing the interaction inserted polar hydrogen. The three-dimensional grid of size $66 \times 56 \times 54$ Å is used with 3D coordinates (4.402, −8.060, and 8.874) to define the region of interactions. The final prepared models and ligands were docked with AutoDock vina. The binding affinity and RMSD values were also calculated. A binding affinity of −7 kcal/mol was set as the threshold for screening the best-docked models. Models with binding affinity <−7 kcal/mol and 0.00 RMSD value were selected for further detailed study. The selected docked models were visualized in the discovery studio.

3. Results

3.1. Identification and physiological properties ABC transporter genes

The genome-wide recognition of ABC transporter genes in *A. cerana* identified 28 a total of ABC transporter genes. Although all proteins contain conserved ABC transporter domains, they showed high diversity in their sequences. The details of all 28 ABC transporter proteins, including molecular weight, protein length, and IP, are mentioned in Table.1. The encoded proteins' length was ranged from 145 to 1749 amino acids; the molecular weight was from 16.043 to 200.874 kDa and the IP from 5.97- 9.5.

3.2. Multiple sequence alignment and phylogenetic analysis of ABC transporter genes

The multiple sequence alignment demonstrated that many important residues and structural motifs, e.g., L_4XXG_8, GXXGXGK, LSGG, R_{45}, A_{49}, DEPTXXVD, were conserved throughout the ABC transporters (Fig. 1). All ABC transporters' combined unrooted phylogenetic tree was categorized into eight major groups (ABCA, ABCB, ABCC, ABCD, ABCE, ABCF, ABCG, and ABCH) with one MRP (Fig. 2). The ABCA group consists of only one gene, i.e., XM_017050518.2. Similarly, ABCC has five genes including *XM_017055838.2*, *XM_017061132.2*, *XM_028668368.1*, *XM_017049887.2*, and *XM_017064673.2* and the ABCD has two genes (*XM_017048648.2* and *XM_017066360.2*). The ABCE has three, and ABCF has six ABC transporters.

3.3. Gene structure organization

As presented in Fig. 2, the number, distribution, and length of introns and exons were not immensely different among the entire gene family. The exons ranged from 4 (XM_028668368.1) to 30 (XM_017055838.2). However, some genes such as *XM_017061551.2* and *XM_028668147.1* have a similar number of exons (13 exons). In addition, XM_028665983.1 and XM_028669661.1 genes have 14 exons but differ in sequence length (Fig. 3).

3.4. Conserved motif analysis

The ABC transporter proteins structure was also investigated amino acid sequences. The MEME motif analysis identified several common and unique motifs in *A. cerana* ABC transporters. Commonly shared motifs usually tended in the same groups indicating similar functions. In the present study results 1st motif was observed in all genes except XM_028666551.1. motif_2nd was present in 26 genes out of 28 genes (excluding XM_028668645.1. and M_028668368.1), motif_3rd was observed in XM_017061132.2, XM_017064673.2, XM_017061950.2, XM_028664559.1, XM_017055838.2, XM_028665690.1, XM_028668368.1 and XM_017053731.2 while motife_4th was observed in XM_017061132.2, XM_017064673.2, XM_017061950.2, XM_017049887.2, XM_028669553.1, XM_028664559.1, XM_017055838.2, XM_028665690.1 and XM_017053731.2. Motifs_5^{th,} was observed in seven genes (XM_017061950.2, XM_028669553.1, XM_028664559.1, XM_017055838.2, XM_028665690.1, XM_017053731.2 and XM_017048648.2), motif_6th was observed in eight genes. Motif_7 and motif_8th was present in eight genes. In summary, some motifs were family-specific, some group-specific, some clade-specific, and some texa specific. The length of motifs was also varied motif to motif like motif_1st had 32 amino acids (aa), motif_2nd had 20 amino acids. We found the motif_3rd, 5th and 10th motifs had 50 amino acids while motifs 4th and 9t^{h} had 41aa.Motif 6th had 47 while 7th and 8th motif had 21 amino acid (Fig. 4).

3.5. Comparative synteny analysis identified ABC transporters

The comparative synteny study analysis among *A. cerana*, A. dorsata, and A. mellifera established a significant relationship in gene evolution, function, triplication, duplication, and expression. It was observed that the *A.cerana XM_028668147.1* gene sequence illustrated synteny with the A. dorsata 0298gene sequence.

Table 1
List of identified putative *Apis cerana* ABC transporter and their features.

Gene Name	Direction	Location	Number of Amino acid	Molecular weight	Theoretical IP
>XM_017061551.2	F	796074..805212	740	81906.92	8.89
XM_017063007.2	R	567283..579217	642	72854.11	8.89
XM_028665683.1	R	55981..80472	725	81281.68	8.9
>XM_028668147.1	F	5955..20683	551	61745.34	8.54
XM_017050518.2	R	47790..81067	1714	192140.26	6.42
>XM_017061132.2	F	508983..526137	838	95774.71	8.73
XM_017064673.2	F	1538530..1594830	1343	147509.33	7.55
XM_028665983.1	R	1226532..1261847	805	90082.76	7.8
XM_028668645.1	R	217429..225638	819	91363.57	8.73
XM_017061950.2	R	508195..514207	1353	154313.22	7.15
XM_017049887.2	F	1072516..1080221	563	62026.41	8.64
XM_017055525.2	F	460683..463560	632	71734.17	6.45
XM_028669553.1	R	522377..533959	1529	173178.59	8.72
XM_028664559.1	R	161942..171891	1355	154074.8	9.02
XM_028669661.1	R	302610..345481	692	77749.69	5.97
XM_017055838.2	R	157528..169083	1749	200874.45	8.87
XM_017051631.1	R	554..3234	537	60497.85	6.55
XM_017066491.2	R	290738..294566	660	74101.02	7.95
XM_017063262.2	F	670930..675028	608	68433.37	8.2
XM_028665690.1	R	2652612..2671553	1291	147672.18	8.62
XM_017065726.2	F	281223..284775	632	71779.29	6.86
XM_028668368.1	R	357224..358882	145	16043.47	7.75
XM_017053731.2	R	694329..704860	1392	156778.59	8.73
XM_017048648.2	F	313141..317381	664	76784.13	9.5
XM_017066360.2	R	470837..474449	758	84479.03	9.22
XM_028666551.1	F	70816..84595	514	59832.66	8.98
XM_017054061.2	R	1242287..1248580	1180	135486.49	6.24
XM_017059994.2	F	72744..77785	1296	150493.92	6.76

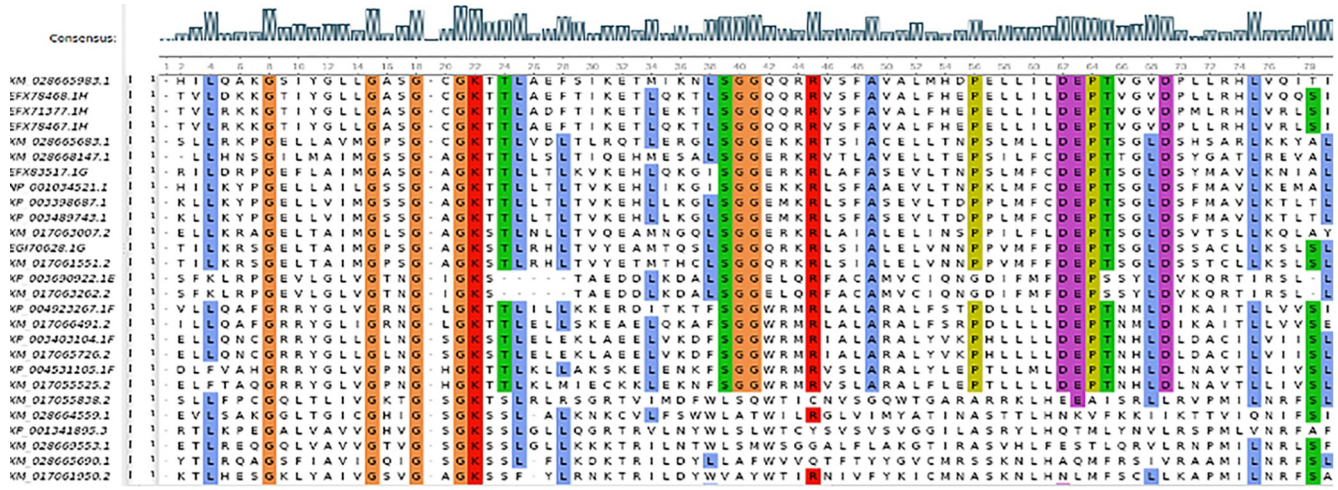

Fig. 1. The multiple sequence alignment.

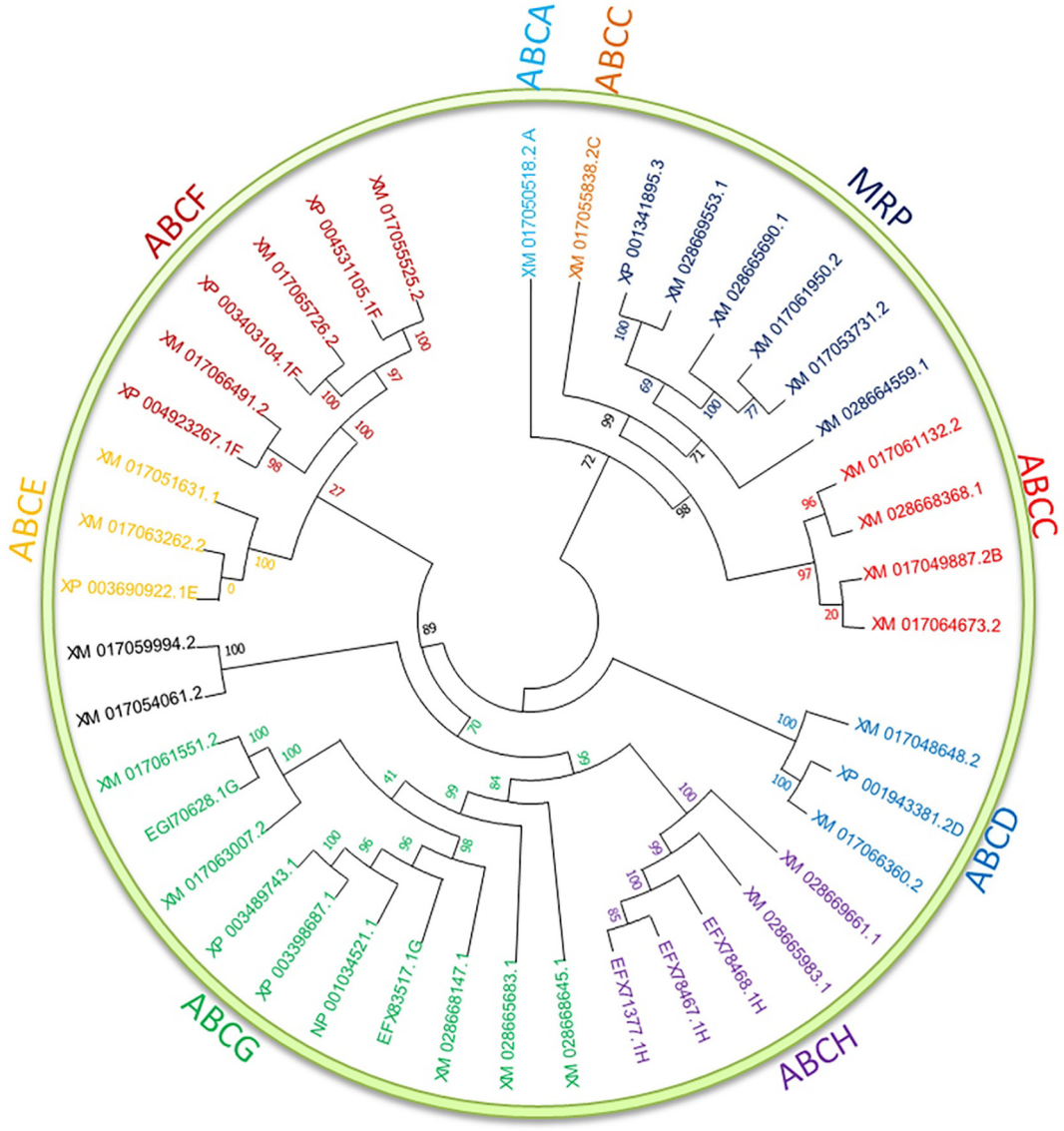

Fig. 2. A phylogenetic tree categorized into eight major groups.

Fig. 3. Distribution of exons, introns, and UTR (untranslated regions) in *Apis cerana* ABC transporters gene sequences.

A. cerana gene sequence *XM_028668147.1* demonstrated synteny with *A. mellifera gnl|Amel_HAv3.10256* (Fig. 5).

3.6. Protein-protein interaction network analysis

The PPI network identified the hubs protein of ABC transporters. The ABCC5; XM_017055838.2, ABCG4; XM_017063007.2 and ABCB7; XM_028668368.1 demonstrated strong interaction network among all ABC transporters. In addition XM_017063262.2 had highest number of interaction with other ABC proteins. The XM_017063262.2 interacted with XM_017048648.2, XM_017061132.2, XM_017066491.2, XM_028668368.1, XM_017064673.2, XM_017065726.2 and XM_017055838.2. Similarly ABCC5;XM_017055838.2 showed interaction with ABCB7;XM_028668368.1, ABCG4;XM_017063007.2, XM_017055525.2, and XM_017065726.2 (Fig. 6).

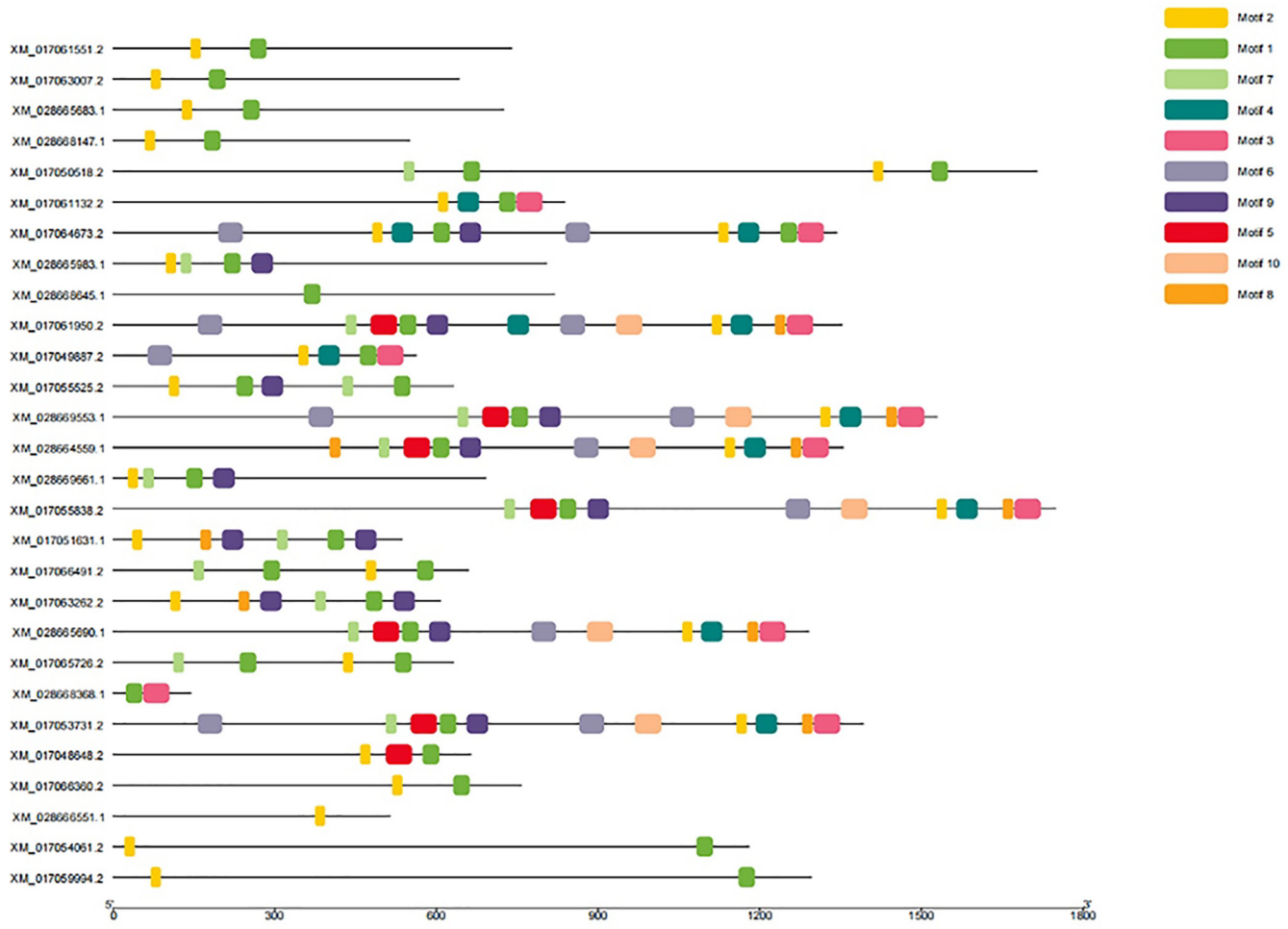

Fig. 4. De novo MEME motifs' distributions in the *Apis cerana* ABC transporters proteins.

3.7. Three-dimensional (3D) protein modeling and molecular docking analysis

Based on the PPI results, we selected three ABC transporters from three ABC groups like ABCG4, ABCC5, and ABCB7. The Swiss model predicted the 3D structures demonstrated that ABCG4 (XM_017063007.2) consists of two chains, A and B, while the other two proteins, ABCC5 (XM_017055838.2) and ABCB7 (XM_028668368.1), had only a single chain. The ribbon and surface structure of ABCG4 presented the dimer formation of the two chains making a complex structure for their functions. We can also conclude that the different ABC transporters groups had different 3D structures, which shows their functional diversity (Fig. 7).

Furthermore, these proteins structures were also evaluated for their interaction with ATP molecules. The transmembrane proteins (ABCC5; XM_017055838.2, ABCG4; XM_017063007.2 and ABCB7; XM_028668368.1) docked with the ATP and their binding affinity are given Figure. Of these proteins, the ABCG4 showed the lowest binding affinity with −7.3 kcal/mol and interacted with ATP by residues Asn_{114}, Asn_{116} Glu_{117}, Phe_{118}, Arg_{119}, Arg_{356} $Gly_{359,}$ and Arg_{457}. Similarly, ABCC5 had the binding affinity of −7.4 kcal/mol and interacted with ATP by Pro_{1271}, Ser_{1273}, Gln_{1490}, Asp_{1491}, Arg_{1554}, Leu_{1556}, Val_{1570} residues. The ABCB7 showed the highest binding affinities with −7.5 Kcal/mol and residues Arg_{69}, Thr_{72}, Ser_{77}, Val_{79}, Asp_{89}, Ser_{90}, Asp_{91}, and $Glu_{92.}$ (Figure). The comparison among the three groups of ABC-transporter protein, e.g., ABCB, ABCC, and ABCG, demonstrated different active sites and binding affinity with ATP molecules. IN summary, the ABCB group has a strong interaction with ATP molecules, followed by ABCC and ABCG (Fig. 8)

4. Discussion

Honey bee A. cerana is one of China native bee species. A. cerana and A. mellifera are close relatives, A. cerana showed different characters compared to A. mellifera. Therefore, A. cerana illustrated strong resistance against Varroa destructor (mite) and getting nectar from flower resources.

All ABC transporter genes were classified into eight groups: ABCA, ABCB, ABCC, ABCD, ABCE, ABCF, ABCG, and ABCH. ABCC proteins subfamily has multiple functions, including ion transport, cell surface receptors, and a wide range of substrate translocation from drug to endogenous compounds (Fukuda and Schuetz, 2012; Tian et al., 2017). The human ABCC subfamily members mentioned to MRPs (multidrug resistance-associated proteins) act as sulfonylurea receptors and are involved in potassium channel regulation, transmembrane cystic fibrosis conductance regulation, and chloride channel construction. ABCD family members belong to half-transporter and import acylCoAs and fatty acid into cell organelle (Theodoulou et al., 2006). It is also involved in peroxisome-related development in Caenorhabditis elegans (Petriv et al.,

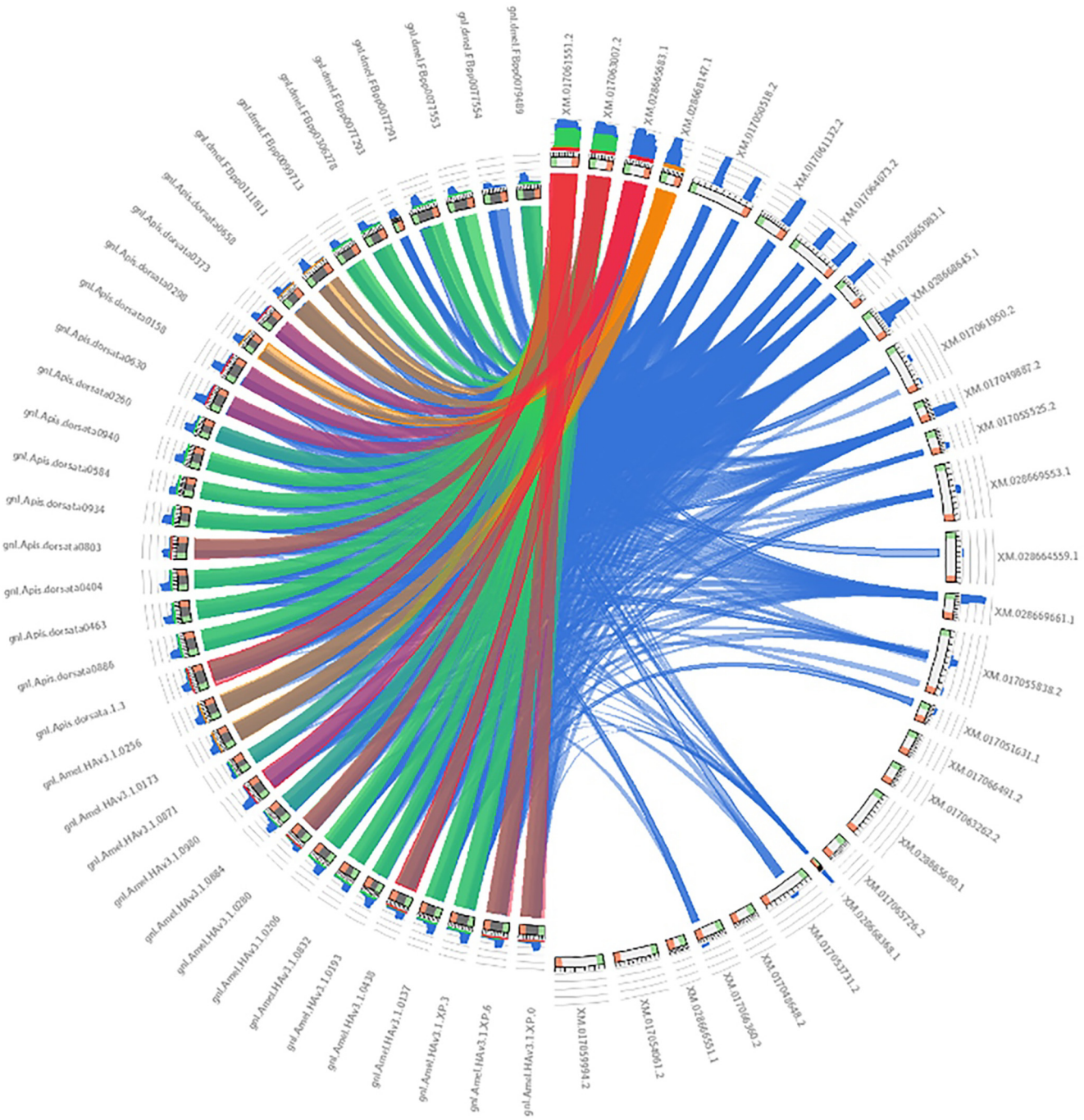

Fig. 5. Synteny analysis among *Apis cerana, A. dorsata,* and *A. mellifera.*

2002). Further, the ABCE transporter family in yeast and human plays a vital function in translation initiation (Zhou et al., 1993). While the other two transporters, ABCE and ABCF, were not described in invertebrates. In penultimate larvae *(Tribolium* castaneum) significant mortality occurred when knocked down TcABCE-3A (ABCE) gene with RNAi approach (Broehan et al., 2013). In addition, *A. cerana* containing ABCG transporter protein showed the largest member of ABC subfamily (include 23 members), similar findings were also reported in *Diuraphis* noxia (Nicholson et al., 2015), *Cimex lectularius* (bed bug), *Anopheles gambiae* (Roth et al., 2003), *Drosophila* (Dean et al., 2001), *A. mellifera (*Liu et al., 2011*)*, and *Pediculus humanus* (body louse in humans) (Lee et al., 2010). Sturm et al. (2009) reported that in the *D. melanogaster* and *D. pulex* genome, the ABCG transporter expansion result from specific lineage gene duplication (Sturm et al., 2009). The ABCE and ABCF subfamilies consist of unusual ABC transporter proteins, identified through NBDs pair link without TMDs. Thus, their structure was oblique their significance in the biological process rather than transportation. The ABCE1 is considered one of the vital conserved proteins in evolutionary relation and is observed in all organisms except eubacteria. Due to its important role in ribosome synthesis and translation, ABCE1 is vital for entire life stages (Barthelme et al., 2011). The RNase L/ABCE1 of *Homo* sapiens was primarily identified as an RNase L inhibitor. *A. cerana* has ten ABCG transporters. The ABCGs have a distinct reverse domain architecture with NBD-TMD (NBD restricted on N-terminus and other is TMD

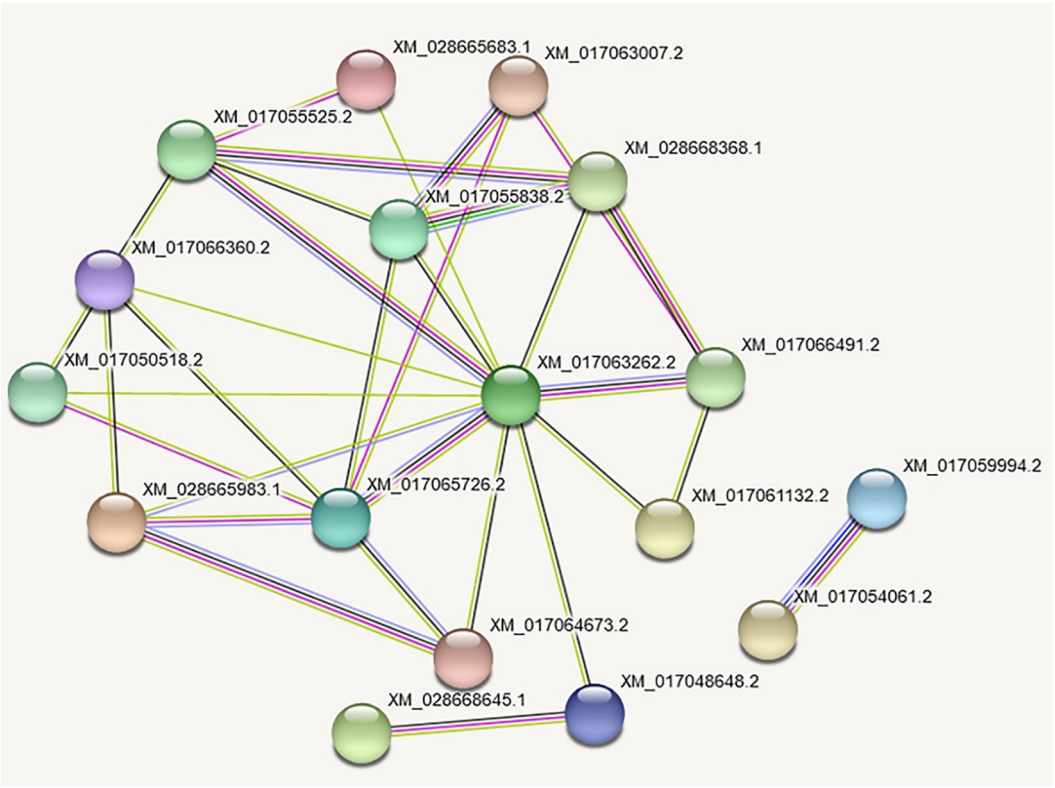

Fig. 6. The PPI network identified the hubs protein of ABC transporters.

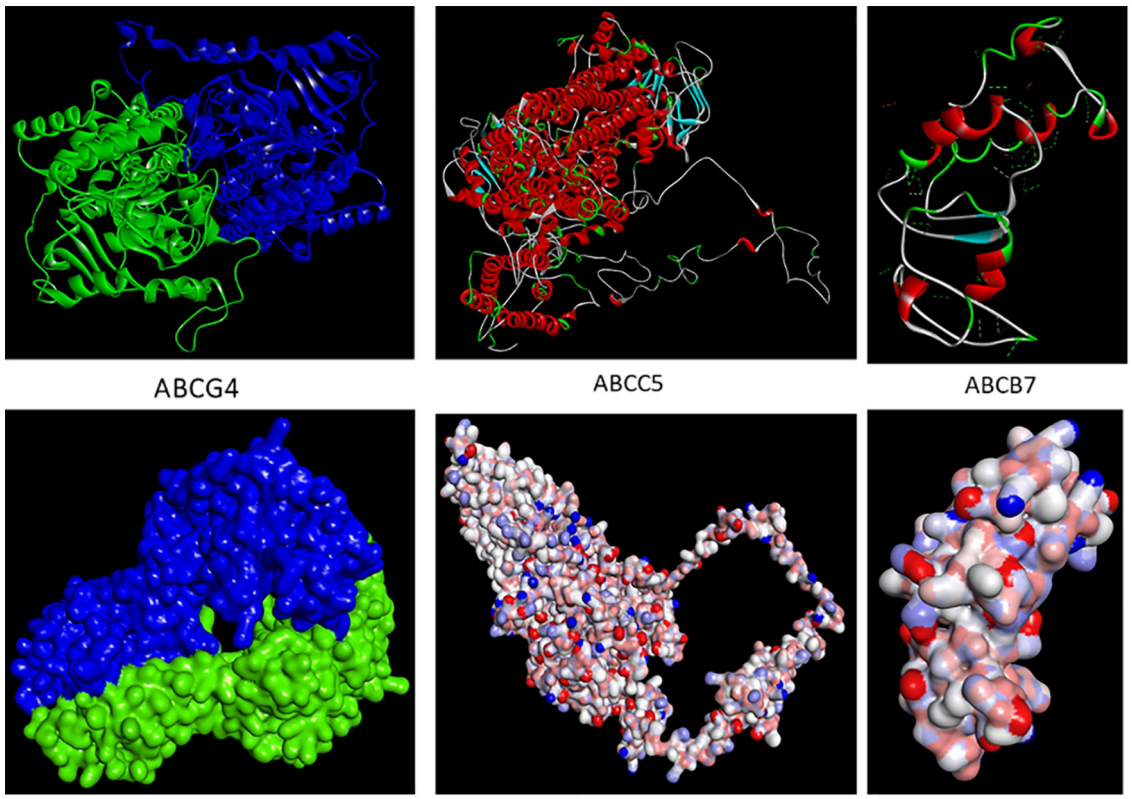

Fig. 7. Three dimensional structure of ABC transporters.

localized at C-terminus). In metazoans, the ABCG transporter considers half-transporters, while after dimerization, it works as functional transporters. Moreover, the ABCGs transporters in fungi and plants are full-transporters and known as PDRs (pleiotropic drug resistance protein) (Kovalchuk and Driessen, 2010). In this study, due to their duplicated structure domain, the PDRs yeast was not

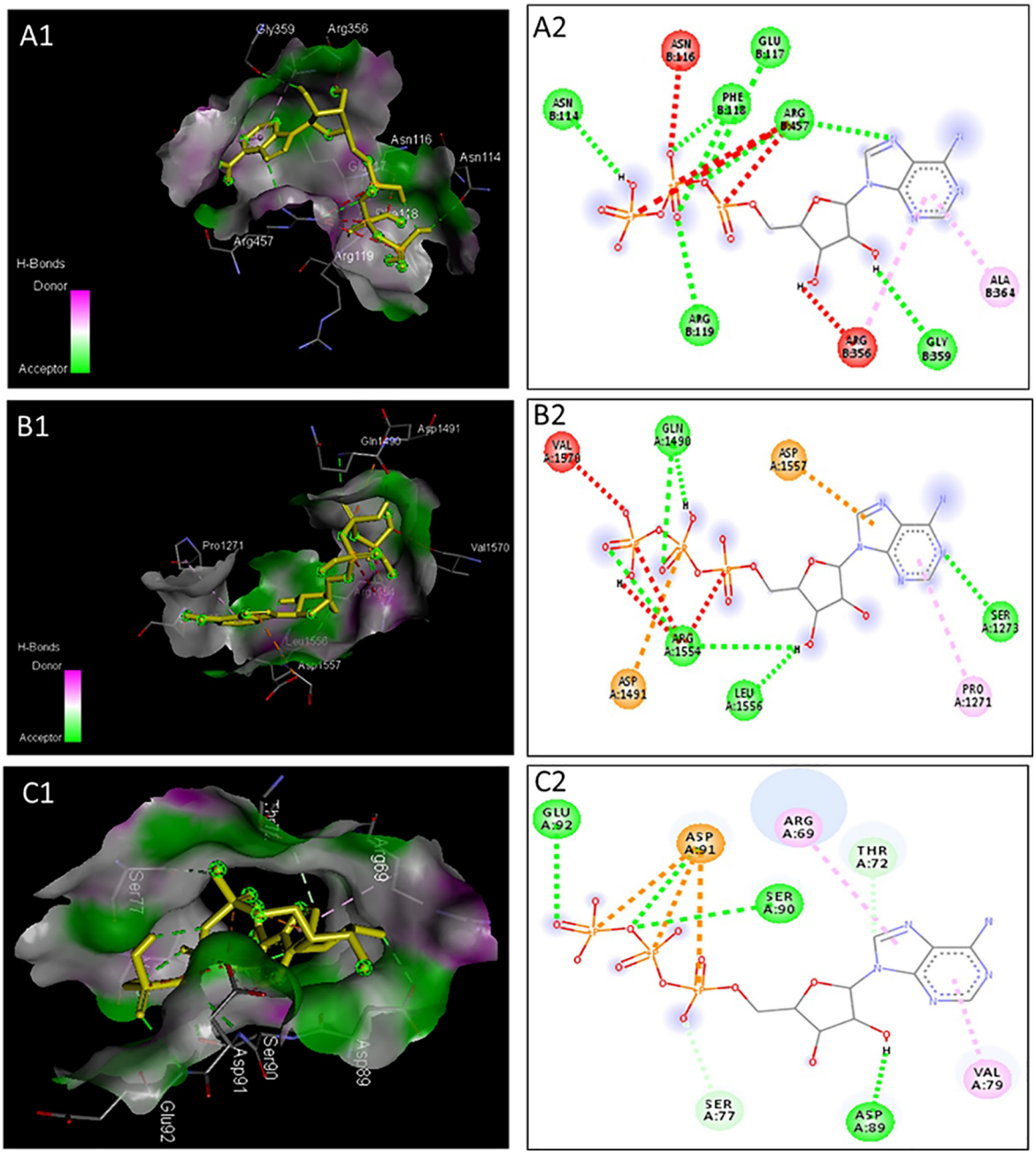

Fig. 8. Molecular docking of *Apis cerana* ABC transporters.

integrated with the phylogenetic analyses tree. Similar to other groups, *A. cerana* has five ABCH transporter, which contains inverse half-transporter that share similar architecture domains identical to ABCG transporter. It was first identified in *D. melanogaster*, which was only annotated in zebrafish and arthropods (Dean and Annilo, 2005).The ABCH transporter is not studied in mammals, plants, fungi, and *C. elegans* (Dean et al., 2001).It was studied in zebrafish but not identified in fungi, cod, and catfish (Liu et al., 2013).

The *D. melanogaster* RNAi screening illustrated that CG9990 *D. melanogaster* gene silencing was lethal (Mummery-Widmer et al., 2009). The ABCH (Px014955) was abundantly up-regulated in two insecticide-resistant strains of *P. xylostella*, (You et al., 2013). In *T. castaneum, TcABCH-9C* knockdown resulted in a hundred percent larval mortality and significantly reduced hatching and fecundity rate. Additionally, the *T. castaneum* larvae injected with dsRNA of *TcABCH-9C* showed it is involved in waterproof barrier formation in epicuticle (Broehan et al., 2013). The ABCH subfamily expression in cotton bollworm *Manduca sexta* and *Helicoverpa armigera* was vastly induced after treating secondary metabolites (Koenig et al., 2015). The ABC transporter gene structural analysis will be useful in protein functional analysis. Evolutionary background disclosed that exon-intron sequence had figured the evolutionary tree of gene family (Zaynab et al., 2021). Later on, it corresponds to prior scientific approaches retained in some plant genes that may contain no introns or short introns at the period of evolution (Zaynab et al., 2021).

Moreover, the firm gene structure may show a quick-expression response to endogenous and exogenous stimuli. Overall structural analysis suggested that ABC transporter genes showed a similar

intron/exon with homogenous functional characters because they originated from duplication events during evolutionary activity. The MEME motif analysis identified several common and unique motifs in *A. cerana* ABC transporters. Commonly shared motifs usually tended in the same groups indicating similar functions (Cao et al., 2005).

5. Conclusion

The genome-wide study identified twenty-eight ABC transports encoding genes in the *A. cerana (Ac)* genome. The phylogenetic analysis revealed that AcABCs are also divided into eight groups similar to other organisms. Of these groups, ABCGs were the largest group in *A. cerana* genome. Different additional computational analyses provided essential data for further functional validation. The sequence associated with structural and functional motifs also showed some common and unique features in ABCs. These identifications might present new insight for advanced functional analysis on the ABC gene group in the *A. cerana* genome.

Declaration of Competing Interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The author appreciates the support of the Research Centre for Advanced Materials Science (RCAMS) at King Khalid University Abha, Saudi Arabia through project number KKU/RCAMS/G002-21. I also thank Dr. Madiha Zaynab for her continous assistannce and useful suggestions during the preparation of this manuscript.

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