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Original Article

In Silico simulation and analysis of human p53 and non-human translationally controlled tumor protein

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Abstract

Translationally controlled tumor protein (TCTP) is a highly conserved protein found in various organisms and eukaryotes and is broadly expressed in several tissues. TCTP plays a key role in preventing apoptosis and promoting cell survival. The conserved tumor suppressor p53 is a transcription factor which responds to stress signals. p53 controls apoptosis through a series of quantitative and qualitative events which require several binding partners including TCTP. However, the exact coordination of these two molecules in the apoptosis pathway is not clearly understood. In this study, docking simulation successfully identified the binding sites of "human TCTP and human p53", "Crustacean, *Penaeus monodon* TCTP and human p53", and "plant, *Elaeis guineensis* TCTP and human p53" with binding energies of -843.10 Kcal/mol, -747.80Kcal/mol, and -786.80 Kcal/mol, respectively. The results implied that non-human TCTPs have less binding activities with human p53 and they are not effective partners compared with human TCTP.

Keywords: TCTP, p53, apoptosis, interaction mechanism analysis, molecular docking

1. Introduction

The mammalian homolog of translationally controlled tumor protein (TCTP) was described in the 1980s (Thomas & Luther, 1981; Yenofsky, Bergmann, & Brawerman, 1982). Later on, it was named as TCTP on the basis of the initial isolation history from the human mammary tumor cells and observation of mRNA expression at the translational level (Böhm *et al.*, 1989). According to the isolation sources and functional specificity (Thomas & Luther, 1981; MacDonald, Rafnar, Langdon, & Lichtenstein, 1995; Yenofsky *et al.*, 1982), TCTP is also known as q23, p21, histamine-releasing factor (HRF), fortilin, and TPT-1, which is highly conserved in nature (Brioudes, Thierry, Chambrier, Mollereau, & Bendahmane, 2010; Thaw *et al.*, 2001) and significantly expressed in a diverse range of tissues and cell types (Yang *et al.*, 2005).

TCTP has been found to be widely associated with an array of diverse biological functions such as calcium binding (Graidist *et al.*, 2007), microtubule stabilization (Bazile *et al.*, 2009; Cucchi *et al.*, 2010), cell growth and regulation (Kim, Jung, & Lee, 2009). The most extensive studies on the function of this protein have been involved with cell survival. Li, Zhang, and Fujise (2001) demonstrated that TCTP has an anti-apoptotic function. In the meantime, it is found that overexpression of TCTP cannot only inhibit

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caspase-3-like activity, but also protect HeLa cells from etoposide-induced apoptosis with TCTP interacting with two anti-apoptotic proteins of the Bcl-2 family: Mcl-1 (Liu, Peng, Cheng, Yuan, & Yang-Yen, 2005; Zhang, Hu, Fadeel, & Ernberg, 2002) and Bcl-xL (Yang *et al.*, 2005).

Structurally, TCTP shares some similarities with proapoptotic Bcl-2 family protein, Bax. Apart from interfering with the dimerization of Bax via inserting itself into mitochondrial membranes (Susini *et al.*, 2008), TCTP affects tumor suppressor p53, whose overexpression induces apoptosis in cancer cells (Vousden & Lane, 2007). A number of studies have shown that the association and interaction between TCTP and p53 prevent apoptosis by destabilizing p53 (Rho *et al.*, 2011). TCTP promotes p53 degradation and MDM2-mediated ubiquitination by competing with NUMB for binding to p53-MDM2 (Amson *et al.*, 2012). On the other hand, TCTP inhibits p53-dependent apoptosis by suppressing the transcriptional activation of the Bax gene (Chen *et al.*, 2011). In addition, p53 up-regulates the transcription of Tpt1, which reduces oxidative stress, minimizes apoptosis, and promotes cell survival in response to a challenge with H_2O_2 (Chen *et al.*, 2013).

Tumor protein p53 is known as p53 or tumor suppressor p53. p53 is a coded protein that regulates the cell cycle and hence functions as a tumor suppressor. It is very significant for cells in multicellular organisms to suppress cancer (Jain *et al.*, 2012; Matlashewski *et al.*, 1984; Surget *et al.*, 2014). Furthermore, an activated p53 protein plays a pivotal role in various signals responsible for activating the repairing proteins and can incarcerate growth by holding the cell cycle (Bourdon *et al.*, 2005; Bourdon, 2014; Laptenko & Prives, 2006). It can instate the programmed cell death related to inducing the apoptosis pathway (Zhu *et al.*, 2000).

According to Amson *et al.* (2012), the experimental results show a decreased number of tumor cells by TCTP knockdown and the combination of TCTP and p53 which lead to the occurrence of cell death (apoptosis). TCTP has been shown to play the physiological role in events and also tumor reversion in stress response (Acunzo *et al.*, 2014; Amson *et al.*, 2013). Given the potential of TCTP and the p53 molecule, it has been applied as a new biopharmaceutical therapeutic strategy (Acunzo *et al.*, 2014; Amson *et al.*, 2013; Bae *et al.*, 2017; Baylot *et al.*, 2012)

In our group, TCTP or fortilin was first isolated from hemocytes of viral infected-shrimp *Penaeus monodon* (Bangrak *et al.*, 2002). The protein has molecular structure similar to human TCTP, which has a Ca^{2+} binding site (Bangrak, Graidist, Chotigeat, & Phongdara, 2004; Bangrak, Graidist, Chotigeat, Supamattaya, & Phongdara, 2002). The administration of a recombinant Pm-TCTP protein can protect shrimp from a white spot syndrome virus infection by inhibiting the viral replication that increases the survival of shrimp culture (Nupan, Phongdara, Saengsakda, Leu, & Lo, 2011; Panrat *et al.*, 2012; Tonganunt *et al.*, 2008). Wang and co-worker found that TCTP from the silkworm, *Bombyx mori* (*Bm*TCTP), as a dual-functional protein was involved in both the cellular and the humoral immune response (Wang *et al.*, 2013). TCTP in *Fenneropenaeus indicus* (rFi-TCTP) acts as a stress-induced survival factor that reduces apoptosis during the viral infection (Rajesh *et al.*, 2014). The enhancement of plant TCTP expression in oil palm embryogenic calli resulted in faster multiplication of the embryogenic calli. Recently, the potential uses of this recombinant TCTP in feed additives for aquaculture are well demonstrated (Sinthujaroen, Tonganunt-Srithaworn, Eurwilaichitr, & Phongdara, 2015; Wang, Hu, Hua, Song, & Xia, 2013). Not only in feed additive products, recombinant TCTP was also used for developing new dental supplemental materials that can promote cell proliferation on pulp cells (Kongsaengkaeo *et al.*, 2013; Sangsuwan *et al.*, 2015; Wanachottrakul *et al*., 2014).

As mentioned earlier, human TCTP can bind to human p53 which regulates the apoptosis pathway. Here, we use *in silico* molecular modeling and docking to demonstrate the binding of human p53 to TCTP from other resources. Together with our report that TCTP from crustacean or plant does not induce tumorigenesis in the human cell line (Kewjurat *et al.*, 2018), these results ensure the potential safe uses of TCTP in various applications.

2. Materials and Methods

To depict whether crustacean TCTP and plant TCTP exert the actions in apoptosis via human p53 pathways, molecular docking simulation was employed to compare between human TCTP/human p53, crustacean TCTP/human p53, and plant TCTP/human p53. Three interaction simulations, that included the human TCTP (PDB ID: 2HR9)/human p53 (PDB ID: 2MEJ), crustacean, *Penaeus monodon* TCTP/human p53, and plant, *Elaeis guineensis* TCTP/human p53, were performed at ClusPro 2.0 web server. In the first step, the coordinate files for the docking molecule and the target molecule were prepared. The PDB files of human TCTP and human p53 were retrieved from Protein Data Bank. As of now, no 3D structures of crustacean TCTP and plant TCTP are available in the protein databank. Hence, the 3D models of both TCTPs were created using homology modeling at SWISS-MODEL server (https://swissmodel.expasy.org). The number of residues that participated in the interaction between them and the docking energy values were considered to optimize the interaction performance. By default, the ClusPro 2.0 server (http://cluspro.bu.edu) displayed the top 10 models. The models of the interaction complexity were evaluated using root-mean-square of atomic position (RMSD) value. The top ranking model with the lowest docking energy value was selected for the simulation of interaction.

3. Results and Discussion

The application of the docking program in prediction of detailed molecular interactions between two proteins was previously investigated (Cai *et al.*, 2006; Looger, Dwyer, Smith, & Hellinga, 2003). Among the currently available docking servers, the ClusPro 2.0 server has been widely used (Comeau, Gatchell, Vajda, & Camacho, 2004). Therefore, in this study, the use of a docking simulation through ClusPro 2.0 server served as a justification for elucidating the interaction between TCTP and p53. By means of Rho (2011) and his co-workers' report, the finding clearly showed the prevention of apoptosis as a result of the interplay between TCTP and p53 (Gnanasekar, Gajalakshmi, & Kalyanasundaram, 2009), which also aligns with the indication by Chen *et al*. (2011) that TCTP can be treated as an inhibitor of p53.

The tumor suppressor protein p53 bears 393 amino acid residues that can be divided into four domains: i) the

transcriptional activation domain (amino acid residues 1-40), ii) the sequence specific DNA binding domain (sequence-specific DNA binding (SSDB) amino acid residues 102-292), iii) the oligomerization domain (amino acid residues 324-355), and iv) the C-terminal domain (amino acid residues 367-393) (Levine, 1997). The anti-apoptotic protein TCTP consists of 3 domains: i) domain 1 (amino acid residues 1-70), ii) domain 2 (amino acid residues 71-120), and domain 3 (amino acid residues 121-172).

From the *in silico* analysis of human TCTP and human p53, the binding residues were identified based on their lowest binding energy. Human TCTP residues 1-6, 35-76, and 166-174 were found to interact with human p53 SSDB at residues 230-236, 267-280, 303-310, and 369-375 (Table 1 and Figure 1). The center binding energy and lowest binding energy were -843.10 Kcal/mol and -955.10 Kcal/mol, respectively (Table 1). Crustacean TCTP residues 42-63, 70-80, and 131-137 were found to interact with human p53 SSDB (Table 1 and Figure 2) with the center binding energy and lowest binding energy being -747.80 Kcal/mol and -828.90 Kcal/mol, respectively. The plant TCTP residues 1-6 and 35-45 were found to interact with human p53 at residues 171-176, and plant TCTP residues 161-168 interacted with p53 at residues 267-272 (Table 1 and Figure 3). The center binding energy and lowest binding energy were -786.80 Kcal/mol and -964.80 Kcal/mol, respectively.

The lowest center binding energy and lowest binding energy values are indicators of quality interaction simulation. A better center binding energy (-843.10 Kcal/mol) was found in human TCTP/human p53 than the center binding energy value (-786.80 Kcal/mol) of plant TCTP/human p53, and crustacean TCTP/human p53 (-747.80 Kcal/mol).

Our results are in coordination with Chen *et al.* (2011) who found that p53 SSDB interacted with TCTP domain 1 and TCTP domain 2 (Gaucher, Xun, Michael, & Steven, 2002).

Moreover, we noticed there were two cysteine amino acid residues in human TCTP and one cysteine amino acid residue in plant TCTP. In human TCTP, the residues are located at the amino acid position 28 and position 172, whereas in plant TCTP, only one cysteine is found at position 168. There is no cysteine presence in crustacean TCTP. The presence of two cysteine residues in human TCTP especially the one at the C terminal is crucial to TCTP dimerization (Gnanasekar & Ramaswamy, 2007; Kim *et al.,* 2009; Lucas *et al.,* 2014) in anti-apoptosis pathway.

Taken together, the structural differences of TCTP from various organisms and their binding efficiency to human p53 predicted from this work may imply the difference in their molecular functions. Further laboratory investigations are required to support this *in silico* simulation. The application can be useful for the prediction of protein-protein interaction and their participation in a certain pathway.

4. Conclusions

This study could predict the amino acid residues in the domains of TCTP that interact with residues in p53. The residues reside in TCTP domain 1 and 2, and p53 SSDB domain which were reported earlier by experimental data. Molecular docking can be used efficiently to predict protein-protein interaction and it shows less binding activities of non-human TCTPs and human p53. However, they may not be the effective binding partners. Therefore, non-human TCTPs can be potentially applied for various applications with no deterioration.

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Table 1. The molecular docking simulation of TCTPs and human p53.

Interaction partners, Binding sites		Binding Energy (Kcal/mol)	
		Center	Lowest
Human TCTP (2HR9)	Human p53 (2MEJ)	-843.10	-955.10
1-MIIYR-6 166-LEMEKC-174 35-MVSRTEGNIDDSLIGGNASA EGPEGEGTESTVITGVDIVMNH-76	230-FCQLAKT-236 267-EVVRRCPHHERCSD-280 303-DDRNTFRH-310 369-RVCACPG-375		
Crustacean TCTP	Human p53 (2MEJ)	-747.80	-828.90
42-IELEGANPSAEEADEGTDTTSQ-63 70-IYMRLQETGFQ-80 131-GESMDPD-137	261-QSQHMTEVVR-270 337-SCMGGMNRRPI-347 371-CPGRDRRTEEENL-385		
Plant TCTP	Human p53 (2MEJ)	-786.80	-964.80
1-MLVYQD-6 35-GMLWEVEGKWVIQGAVNVDI-45 161-TDPTFLYFAYGLKEIKC-168	117-SQKGYSWSQFS-127 267-EVVRRC-272		

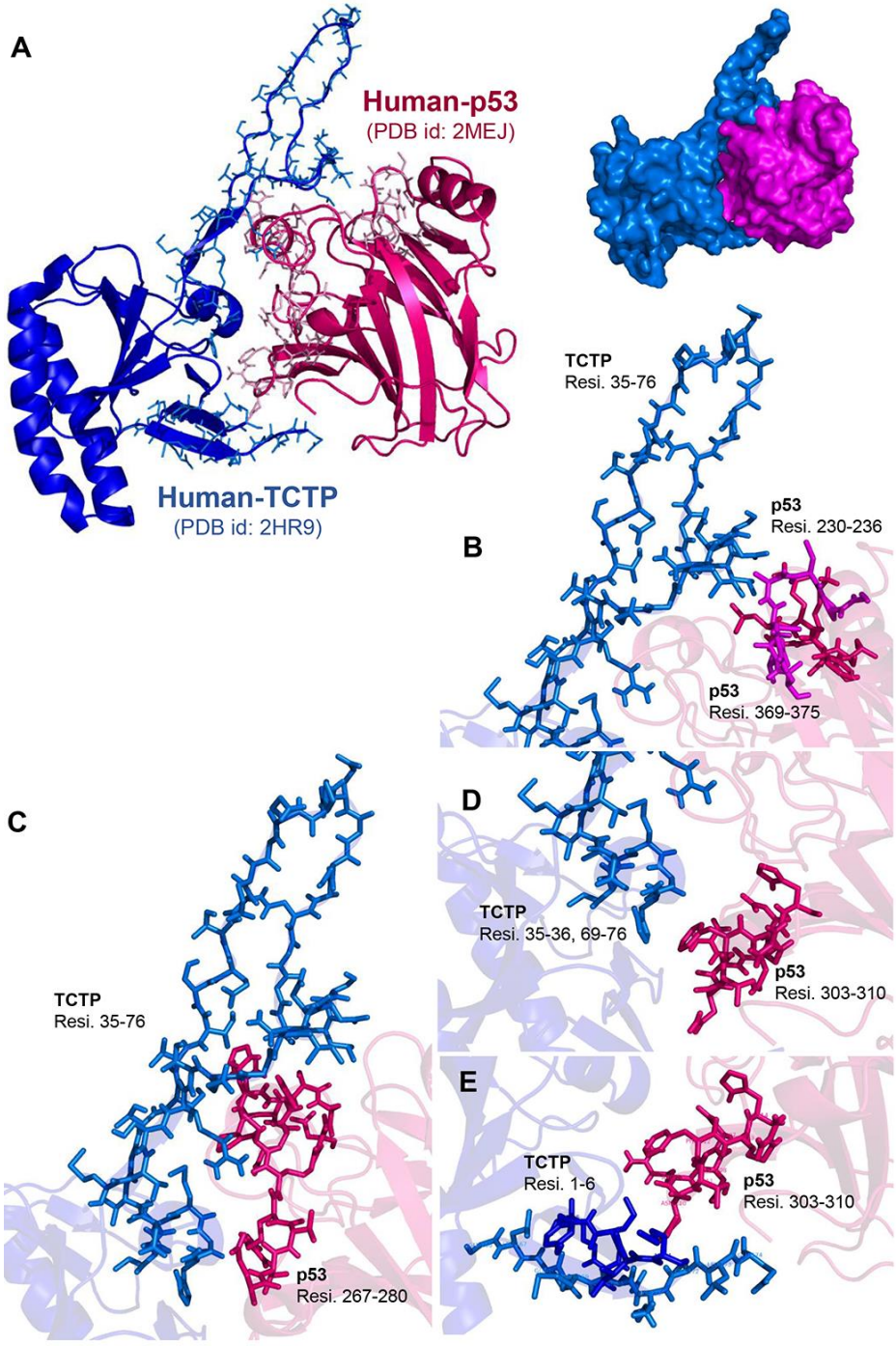

Figure 1. Interaction complexes of human TCTP (PDB ID: 2HR9) and human p53 (PDB ID: 2MEJ).
(A) The interaction complex of human TCTP (blue color) and human p53 (pink color). The interaction binding sites and residues in between human TCTP and human p53 were simulated by ClusPro 2.0 server. The ten lowest binding energy complexes of interaction were selected from the molecular docking simulation during identification of binding site residues. (B) The graphical representation of the binding sites of human TCTP and human p53. The analysis found that the human TCTP residues 35-76 bound to human p53 at residues 230-236. (C) The human TCTP residues 35-76 were also found to bind with human p53 at residues 267-280. (D) The two small regions of human TCTP residues 35-36 and 69-76 showed binding sites with p53 residues 303-310. (E) The graphic shows residues 1-6 on N-terminal region of human TCTP that bind with human p53 residues 230-236.

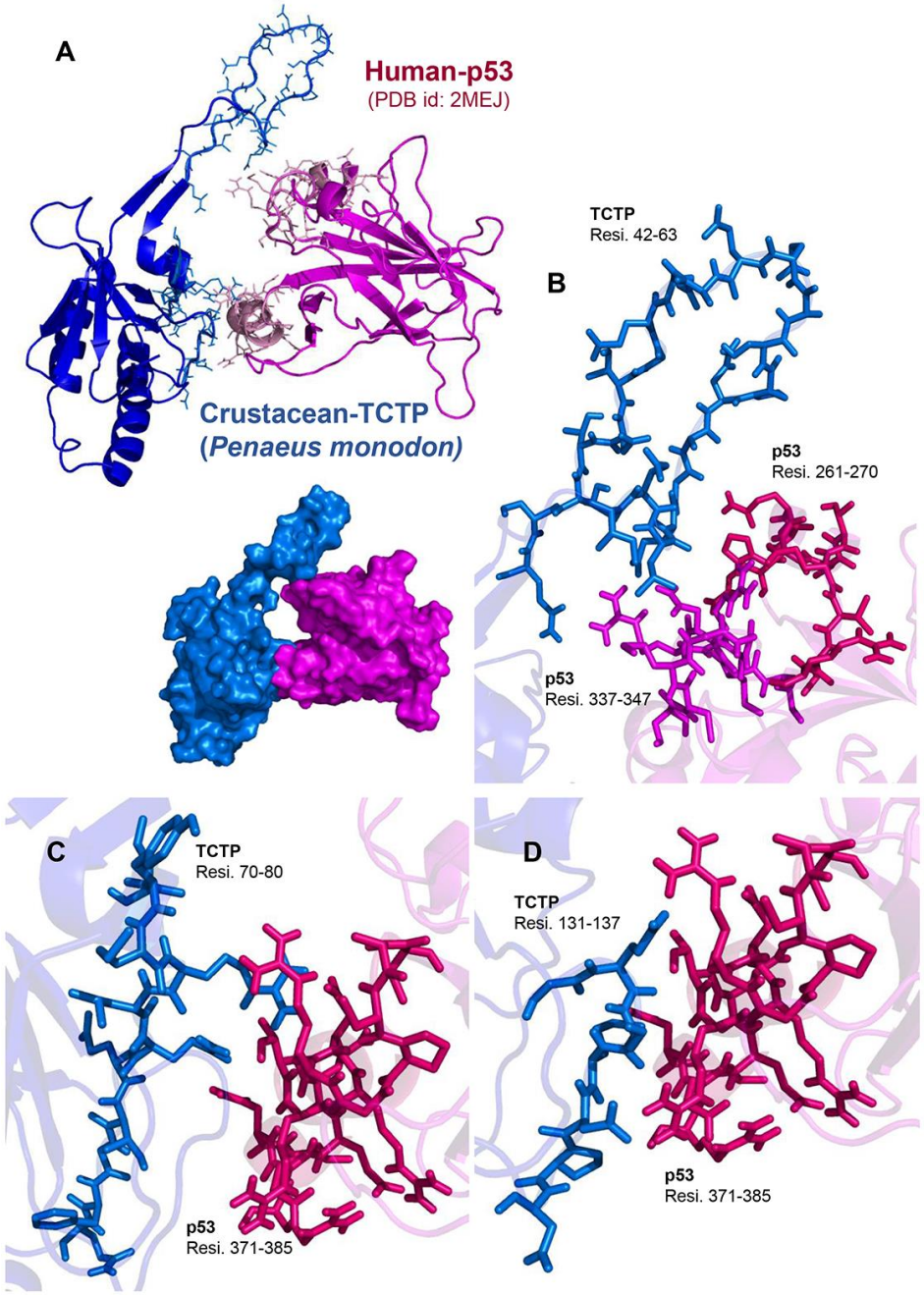

Figure 2. The interaction complexes of crustacean TCTP and human p53 (PDB ID: 2MEJ).
As the solution structure of *Penaeus monodon* TCTP is unavailable at Protein Data Bank, for this interaction simulation we predicted the 3D model from the amino acid sequence of *Penaeus monodon* TCTP (accession no: AAO61938.1) using the homology modeling technique at SWISS-MODEL server. (A) The complex model represents the simulated interaction binding sites between crustacean TCTP and human p53 by the ClusPro 2.0 server. The lowest binding energy complexes were selected for the analysis of binding site residues in details. (B) According to these predictions, the crustacean TCTP residues 42-63 seem to bind with human p53 residues 261-270 and 337-347, respectively. (C) The crustacean TCTP residues 70-80 bind to human p53 at residues 371-385. (D) The human p53 residues 371-385 also have shown the binding sites with crustacean TCTP at residues 131-137.

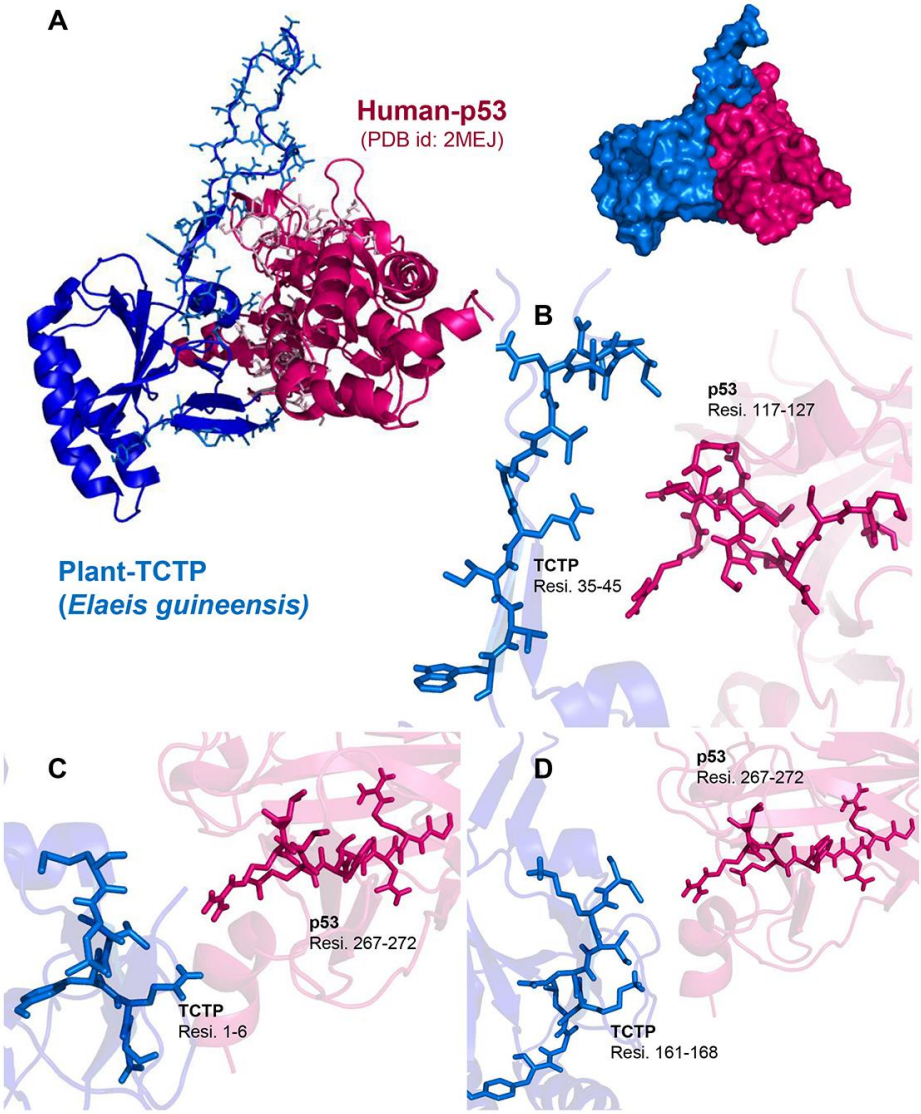

Figure 3. The interaction complexes of plant TCTP and human p53 (PDB ID: 2MEJ).
Same as the solution structure of *Penaeus monodon* TCTP, the 3D model of *Elaeis gunineensis* is also unavailable at Protein Data Bank, the 3D structure of plant TCTP was created from the amino acid sequence of *Elaeis gunineensis* TCTP (accession no: ADM88549.1) using the homology modeling technique at the SWISS-MODEL server and docking simulation using the ClusPro 2.0 server. (A) The interaction complex simulation of plant TCTP and human p53. (B) The binding sites of plant TCTP at residues 35-45 bound to human p53 residues 117-127. (C-D) The human p53 amino acid residues 267-272 showed two different sites of binding with plant TCTP. The human p53 with residue 267-272 bound to residues 1-6 on N-terminal end and residues 161-168 on C-terminal end of plant TCTP.

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