Bioinformation 17(9): 784-789 (2021) ISSN 0973-2063 (online) 0973-8894 (print)

www.bioinformation.net
Volume 17(9)

Research Article

Molecular docking analysis of p53 with Toll-like receptors

Mohammad Jahoor Alam*[1], Fevzi, Bardakci[1], Sadia Anjum[1], Shumayla Rasheed Mir[2], Irfan Ahmad[3] & Mohd Saeed*[1]

[1]Department of Biology, College of Science, University of Hail, Kingdom of Saudi Arabia, [2]College of Computer Science and Engineering, University of Hail, Kingdom of Saudi Arabia, [3]Department of Clinical Laboratory Science, College of Applied Medical Science, King Khalid University, Kingdom of Saudi Arabia; Corresponding author, Mohammad Jahoor Alam j.alam@uoh.edu.sa, Dr. Mohd Saeed - mo.saeed@uoh.edu.sa

Received September 1, 2021; Revised September 15, 2021; Accepted September 15, 2021, Published September 30, 2021

DOI: 10.6026/97320630017784

Declaration on Publication Ethics:
The author's state that they adhere with COPE guidelines on publishing ethics as described elsewhere at https://publicationethics.org/. The authors also undertake that they are not associated with any other third party (governmental or non-governmental agencies) linking with any form of unethical issues connecting to this publication. The authors also declare that they are not withholding any information that is misleading to the publisher in regard to this article.

Author responsibility:
The authors are responsible for the content of this article. The editorial and the publisher have taken reasonable steps to check the content of the article in accordance to publishing ethics with adequate peer reviews deposited at PUBLONS.

Declaration on official E-mail:
The corresponding author declares that official e-mail from their institution is not available for all authors

Abstract:
P53 is one of the most important proteins for its role in cellular signal transduction pathways. It regulates a wide variety of cellular processes, which includes apoptosis, senescence, cell cycle arrest, differentiation, and DNA repair and replication and cancer dynamics. It is a transcription factor for various cellular proteins. Recent report suggests that P53 is linked with transduction proteins involved in cellular immunity. Toll like receptors are needed for communication in cellular immunity. The interaction between p53 and toll like receptors is reported in various studies. Therefore, it is of interest to document the molecular docking analysis of p53 with Toll-like receptors for further consideration in therapeutic development. In the present paper we studied molecular interaction between p53 and toll like receptors using molecular docking approach. We used open-source tools for molecular docking and analyzing the data. Our molecular docking results suggest there is a promising interaction between p53 and toll like receptors. Our study will be a very useful for molecular therapeutics and drug design strategies. Further, molecular dynamics studies can be useful to determine of the stability of complex form by p53 and toll like receptors.

Key words: p53, Toll-like receptor, Interaction, Communication, Docking

Background:
P53 protein act as transcription factor for various cellular proteins such as MDM2, p21, Fas, Bax, p48, PTEN, B99, PAI, related to apoptosis, cell-cycle arrest, senescence, glycolysis, TCA cycle, differentiation, cell fate and suppression of cancer cells progression **[1].** The concentration of p53 protein in cells also varies due to its response to a variety of cellular stress, such as, hypoxia, nucleotide depletion, nitric oxide, DNA damage **[2].** Recently, role of p53 in cellular immunity have been reported **[3].** It is evident that a highly activated form of the p53 protein leads to suppression of inflammation. It is suggested that it activates Toll-like receptors (TLRs) proteins **[4].** Cellular immunity acts as defense systems against bacterial, viral and fungal infections **[5-7].** Moreover, cells have specialized receptor proteins (such as PRRs (pattern recognition receptors)), which are responsible for recognizing antigens such as bacteria, virus, fungus etc, and activating the proteins which are directly and indirectly associated with cellular immunity. Further, PRRs are specialized in functions due to its recognition of repeating patterns of molecular structures of pathogen, known as PAMP (pathogen

associated molecular pattern). TLRs belong to the family of pattern recognition receptors (PRRs) **[6, 8, 9].** TLRs also participate in signaling of various metabolic pathways linked to apoptosis and suppression of cancer progression **[10].** However, the interaction between TLRs and p53 is known **[11]** with molecular interaction data **[12].** Therefore, it is of interest to document the molecular docking analysis of p53 with Toll-like receptors for further consideration in therapeutic development.

Material and Methods:

P53 structure data (PDB ID: 2OCJ) was downloaded from RCSB [https://www.rcsb.org/]. We used discovery studio suit for the removal of unnecessary molecules from PDB structure file. Similarly, we also downloaded PDB structure for all human TLRs (from TLR 1 to TLR 10) [PDB ID: 1FYV (TLR1), 1FYW (TLR2), 2MK9 (TLR3), 2Z63 (TLR4), 3JOA (TLR5), 4OM7 (TLR6), 6LVY (TLR7), 5W3M (TLR8), 5Y3M (TLR9), 2J67 (TLR10)]. Protein-protein molecular docking completed using HADDOCK 2.4 (an open-source tools for molecular docking) available at [https://wenmr.science.uu.nl/haddock2.4/] **[13].** The results obtained from HADDOCK were further analyzed using PRODIGY (an online tool) [https://wenmr.science.uu.nl/prodigy/] **[14]** for finding binding affinity as well as dissociation constant of the protein-protein complex formed by p53 and TLRs as shown in table 1. Moreover, we also collected docking parameters such as HADDOCK score, RMSD from the overall lowest-energy structure, Van der Waals energy, Electrostatic energy, Desolvation energy and Z-Score form HADDOCK tools after completion of docking of each TLR receptor with p53 as shown in table 2. Simultaneously, we also performed molecular docking using PyDOCK (an online server) [https://life.bsc.es/pid/pydock/] **[15]** to further verify the molecular docking interaction between p53 and TLRs. We further finding the stability of p53 and TLRs protein complex using online available statistical split server (SPSERVER) [http://aleph.upf.edu/spserver/] **[16].** The output of the SPSERVER has been tabled in table 3. Various statistical parameters were used such as Pair, Ecomb, Es3dc, Elocal, E3dc, E3d, Zpair, Zecomb, Zes3dc, Zelocal and Ze3dc, to find out the stable complex forming. We also used RStudio statistical package to pot heatmap for the protein-protein interaction between p53 and TLRs.

Table 1: Binding affinity and Dissociation constant

Complex	Binding Affinity (Kcal per mol)	Dissociation constant	Stability
P53-TLR1	-15.1	$8.6x10^{-12}$	Moderate
P53-TLR2	-14.6	$2x10^{-11}$	Moderate
P53-TLR3	-14.1	$4.4x10^{-11}$	Moderate
P53-TLR4	-18.8	$1.7x10^{-14}$	Most stable
P53-TLR5	-13.3	$1.7x10^{-10}$	Moderate
P53-TLR6	-12.9	$3.5x10^{-10}$	Moderate
P53-TLR7	-15.7	$7.1x10^{-12}$	Moderate
P53-TLR8	-18.4	$3.5x10^{-14}$	Most stable
P53-TLR9	-11.1	$7.3x10^{-9}$	Moderate
P53-TLR10	-17.0	$3.5x10^{-13}$	Moderate

Table 2: Obtained results from HADDOCK

Complex	HADDOCK score	RMSD from the overall lowest-energy structure	Van der Waals energy	Electrostatic energy	Desolvation energy	Z-Score
P53-TLR1	249.635.2	11.40.3	-82.92.8	-406.655.8	-3.65	-1.9
P53-TLR2	160.730.1	0.70.5	-1092.7	-430.636.1	-0.42.3	-1.3
P53-TLR3	161.814.9	10.60.1	-63.75.9	-110.69.7	-42.42.5	-1.7
P53-TLR4	318.532.6	1.00.8	-83.113.4	-600.484.7	17.54.4	-2.2
P53-TLR5	263.119.4	11.50.6	-105.48.8	-348.460.5	-8.44.1	-1.9
P53-TLR6	254.99	11.20.1	-91.62.9	-266.719.7	-12.83.4	0
P53-TLR7	301.914.6	11.60	-101.513.1	-334.967.7	7.65.4	-1.4
P53-TLR8	197.77.4	10.20.1	-98.316.2	-42640.7	-1.13.5	-1.7
P53-TLR9	31011	70.4	-769.7	-372.553.5	-6.33.8	-1.8
P53-TLR10	196.216.1	14.10.1	-101.95.1	-384.517.7	-0.92.8	-1.7

Table 3: Global Fold Score:

Fold	PAIR	ECOMB	ES3DC	ELOCAL	E3DC	E3D	ZPAIR	ZECOMB	ZES3DC	ZELOCAL	ZE3DC
P53-TLR1	-45.16	-5210.93	-73.97	30620.70	-66.76	-35690.90	-5.58	-3.30	-5.18	-2.82	-7.19
P53-TLR2	-20.83	-4257.57	-57.29	29334.50	-67.18	-33467.60	-5.20	-3.76	-4.81	-3.34	-6.78
P53-TLR3	-21.13	-3253.20	-19.22	19920.20	-63.28	-23090.90	-3.26	-2.55	-3.43	-2.13	-6.01
P53-TLR4	-101.56	-16148.51	-73.60	69910.50	-717.20	-85268.20	-9.89	-2.53	-7.77	-1.68	-9.21
P53-TLR5	-82.13	-15551.21	-82.44	83571.70	-625.98	-98414.50	-8.62	-4.97	-6.40	-4.17	-12.56
P53-TLR6	-55.69	-4804.99	-75.56	30377.60	-29.53	-35077.50	-6.70	-3.63	-5.94	-3.15	-6.85
P53-TLR7	-147.22	-20841.69	-152.60	87646.90	-901.09	-107434.90	-11.52	-3.80	-10.06	-3.12	-9.36
P53-TLR8	-107.86	-19514.50	-125.96	85242.40	-761.24	-103869.70	-10.30	-3.75	-9.55	-2.98	-9.79
P53-TLR9	-207.68	-18212.90	-152.77	86413.50	-715.53	-103758.10	-11.18	-3.29	-9.69	-2.63	-8.33
P53-TLR10	-54.11	-5359.40	-66.50	29382.00	-70.80	-34604.10	-6.36	-3.92	-4.49	-3.39	-8.07

Results:

We have shown p53 and TLRs interaction obtained from HADDOCK docking in **Figure 1**. It is noticed that that all the TLR protein interact with p53 protein. We observed hydrogen as well as electrostatic bond near the interface between p53 and each TRL as shown in **Figure 1.** It is found that among all interaction between protein-protein, TLR 4 interaction is stable as shown table 1 and table 2. The binding affinity between TLR4 and p53 was found to be -18.8, which is comparatively higher among all interactions. Further, dissociation constant is also comparatively higher for p53 and TLR4 interaction. The higher is the stability constant (dissociation constant), higher is the stability of the complex. Molecular docking results using PyDOCK (online server for protein-protein docking) as shown in figure 2. It is noticed from results shown in figure 2 that there is comparatively strong interaction between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9.

We assessed the stability of the complex formation between p53 and various TLRs proteins using SPSERVER statistical tools as shown in figure 3. We observed that all TLR proteins forms stable complex with p53. Moreover, it is also noticed that from results shown in figure 3 that there is comparatively strong stability between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9 complexes. Heatmap plot, as shown in figure 4, further confirmed the interaction between p53 and TLRs are very prominent. Moreover, it is again noticed that there is comparatively strong stability between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9 complexes.

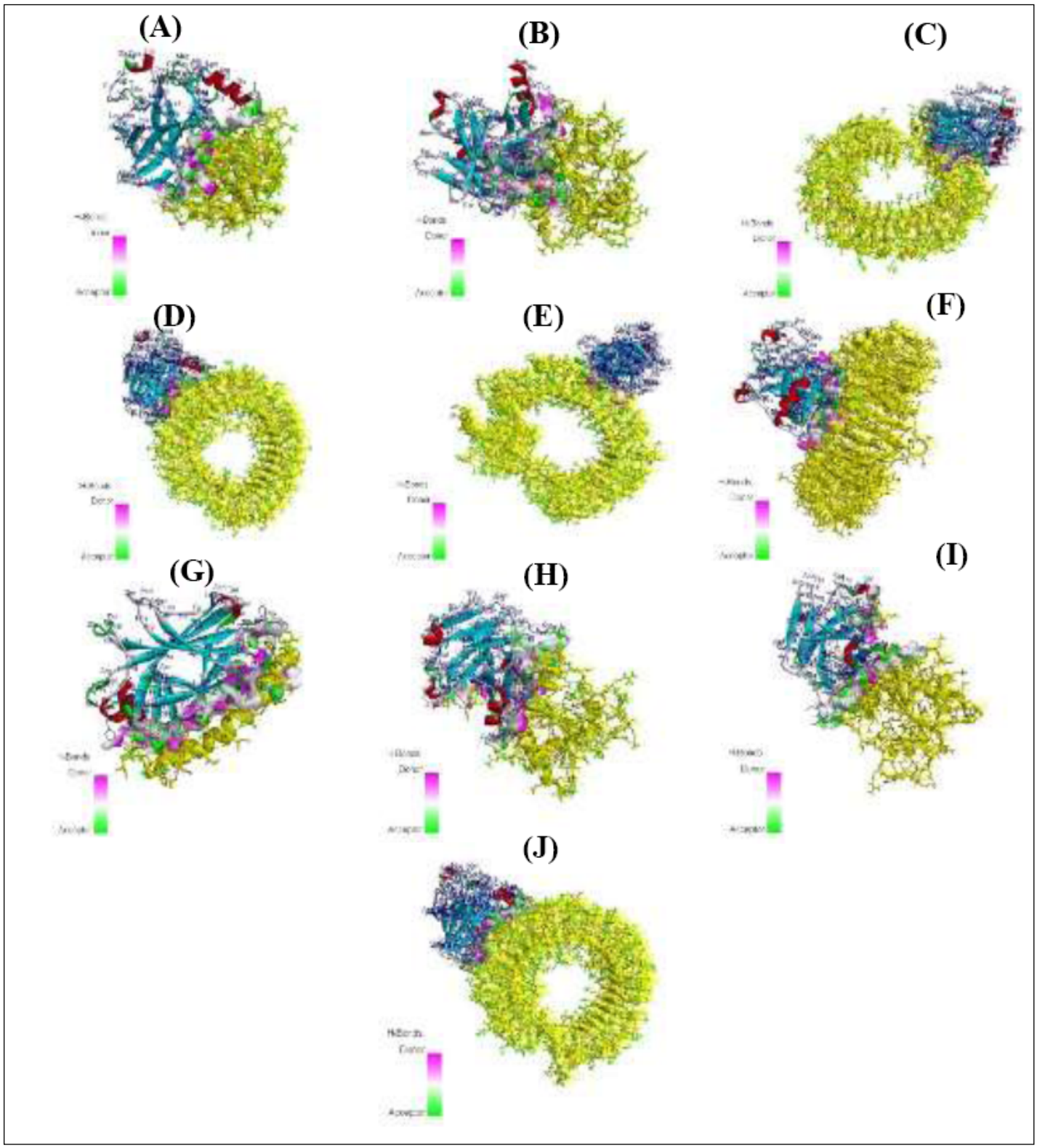

Figure 1: HADDOCK docking output between p53 and TLRs. (A). Docking between p53 (in blue colour) and TLR 1 (in yellow colour) (B). Docking between p53 (in blue colour) and TLR 2 (in yellow colour) (C). Docking between p53 (in blue colour) and TLR 3 (in yellow colour) (D). Docking between p53 (in blue colour) and TLR 4 (in yellow colour) (E). Docking between p53 (in blue colour) and TLR 5 (in yellow colour) (F). Docking between p53 (in blue colour) and TLR 6 (in yellow colour) (G). Docking between p53 (in blue colour) and TLR 7 (in yellow colour) (H). Docking between p53 (in blue colour) and TLR 8 (in yellow colour) (I). Docking between p53 (in blue colour) and TLR 9 (in yellow colour) (J). Docking between p53 (in blue colour) and TLR 10 (in yellow colour).

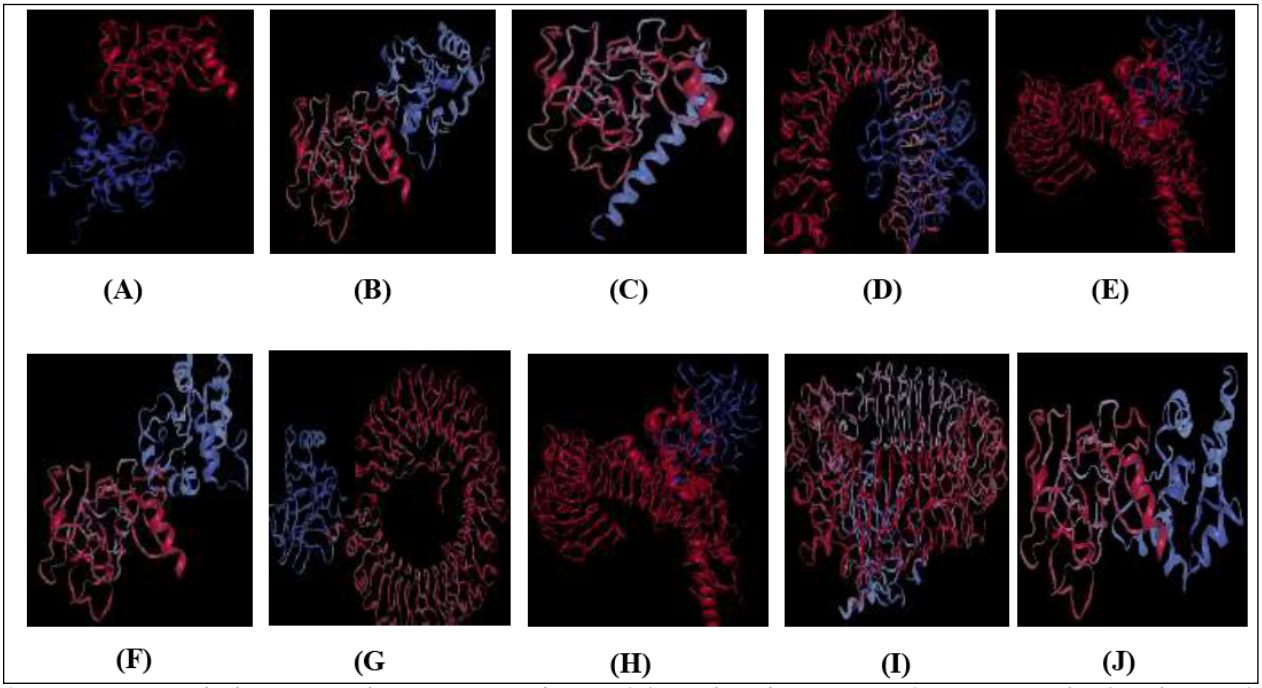

Figure2: PyDOCK docking output between p53 and TLRs. (A). Docking between p53 (in magenta colour) and TLR 1 (in blue colour) (B). Docking between p53 (in magenta colour) and TLR 2 (in blue colour) (C). Docking between p53 (in magenta colour) and TLR 3 (in blue colour) (D). Docking between p53 (in blue colour) and TLR 4 (in magenta colour) (E). Docking between p53 (in blue colour) and TLR 5 (in magenta colour) (F). Docking between p53 (in magenta colour) and TLR 6 (in blue colour) (G). Docking between p53 (in blue colour) and TLR 7 (in magenta colour) (H). Docking between p53 (in blue colour) and TLR 8 (in magenta colour) (I). Docking between p53 (in magenta colour) and TLR 9 (in blue colour) (J). Docking between p53 (in magenta colour) and TLR 10 (in blue colour).

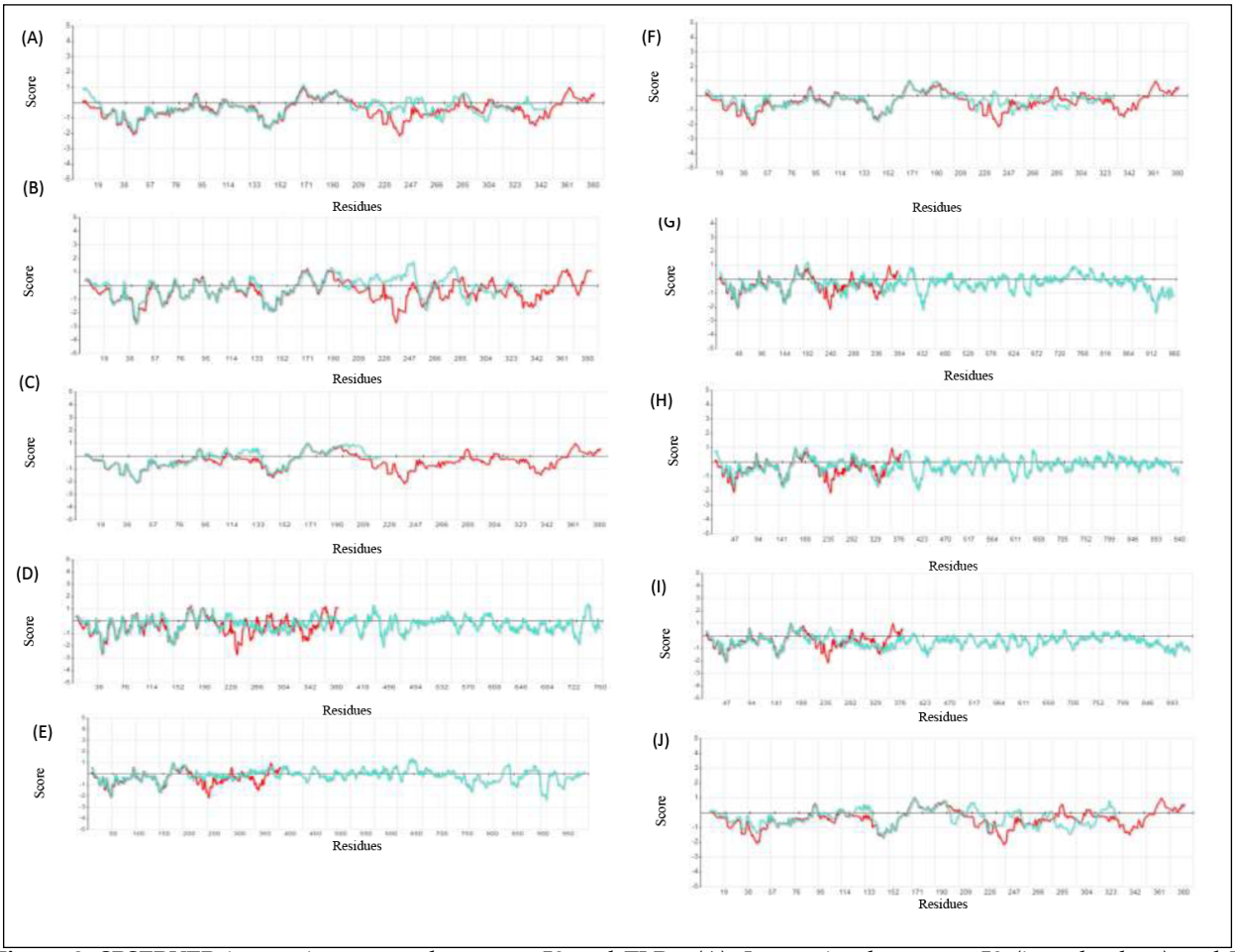

Figure 3: SPSERVER interaction output between p53 and TLRs. (A). Interaction between p53 (in red colour) and TLR 1 (in cyan colour) (B Interaction between p53 (in red colour) and TLR 2 (in cyan colour) (C). Interaction between p53 (in red colour) and TLR 3

(in cyan colour) (D). Interaction between p53 (in red colour) and TLR 4 (in cyan colour) (E). Interaction between p53 (in red colour) and TLR 5 (in cyan colour) (F). Interaction between p53 (in red colour) and TLR 6 (in cyan colour) (G). Interaction between p53 (in red colour) and TLR 7 (in cyan colour) (H). Interaction between p53 (in red colour) and TLR 8 (in cyan colour) (I). Interaction between p53 (in red colour) and TLR 9 (in cyan colour) (J). Interaction between p53 (in red colour) and TLR 10 (in cyan colour).

Discussion:

The role of p53 in apoptosis and cancer is reported in various research literatures **[1,2,17,20, 21].** Moreover, the role of p53 in cellular immunity is still a challenging area of the research **[3,4,22].** Similarly, the role of TLRs is very much studied in cellular immunity **[23-27].** However, role of TLRs in apoptosis and cancer is still few reported [10,28-31]. Docking result suggests that there are strong possibilities of interaction between p53 and TLRs proteins. The HADDOCK docking results in figure 1, suggests that TLR1 to TLR10 proteins interacts with p53 protein. Again, the binding affinity and dissociation constant as shown in table 1 further support the docking results obtained from HADDOCK. The PRODIGY analysis suggests that comparatively strong interaction between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9 complexes. Moreover, PyDock server docking results further suggest that there are interactions between p53 and TLRs proteins as shown in figure 2. The statistical assessment of the stability of complexs between p53 and various TLRs proteins also suggests and support the docking results as shown in figure3. Moreover, statistical analysis results also suggest that there is comparatively strong stability between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9 complexes. Finally, Heatmap plot as shown in figure 4, clarify the interactions between p53 and TLRs proteins. Heatmap plot also suggests that there is comparatively strong stable complex between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9.

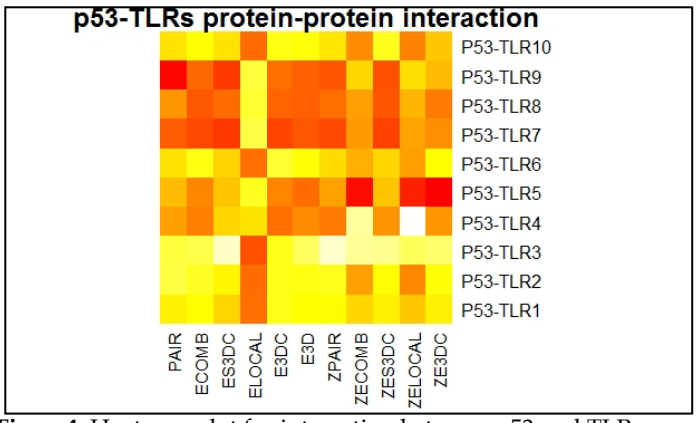

Figure4: Heatmap plot for interaction between p53 and TLRs. Red colour indicating strong interaction and yellow colour indicating least interaction.

Conclusions:

We document the Molecular docking analysis of p53 with Toll-like receptors. Moreover, the interaction between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9 is found to be stable for the understanding of their molecular mechanism. Our study will be a very useful for molecular therapeutics and drug design studies for cellular immunity and cancer. In future path, for more clarity, molecular dynamics studies can be useful to determine of the stability of complex form by p53 and toll like receptors.

Acknowledgements:

This research has been funded by Scientific Research Deanship at University of Ha'il, Saudi Arabia through research project number RG-191347.

References:

[1] Vogelstein B *et al. Nature,* 2000 **408**:307. [PMID: 11099028]
[2] Ozaki T *et al. Cancers (Basel)*, 2011 **3**:994. [PMID: 24212651]
[3] Agupitan AD *et al. Int J Mol Sci*. 2020 **21**:3452. [PMID: 32414156]
[4] Shatz M *et al. Cancer Res*. 201 **72**:3948. [PMID: 22673234]
[5] Vidya MK *et al, Int Rev Immunol*. 2018 **37**:20. PMID: 29028369]
[6] Yamamoto M *et al. Gastroenterol Res Pract*. 2010 **2010**:240365. [PMID: 21197425]
[7] Moresco EM *et al. Curr Biol*. 2011 **21**:R488. [PMID: 21741580]
[8] Sánchez E *et al. Inmunologia*. 2004 **23**:328.
[9] Hug H *et al. Nutrients*. 2018 **10**:203. [PMID: 29438282]
[10] Salaun B *et al. J Immunol.* 2006 **176**:4894. [PMID: 16585585]
[11] Kastenhuber ER *et al. Cell*. 2017 **170**:1062. [PMID: 28886379]
[12] Menendez D *et al. PLoS Genet*. 2011 **7**:e1001360. [PMID: 21483755]
[13] Dominguez C *et al. J Am Chem Soc*. 2003 **125**:1731. [PMID: 12580598]
[14] Xue LC *et al. Bioinformatics*. 2016 **32**:3676. [PMID: 27503228]
[15] Jiménez-García B *et al. Bioinformatics*. 2013 **29**:1698. [PMID: 23661696]
[16] Aguirre-Plans J *et al. BMC Bioinformatics*. 2021 **22**:4. [PMID: 33407073]
[17] Uehara I *et al. Cancers (Basel)*. 2018 **10**:219. [PMID: 29954119]
[18] Frank AK *et al. Mol Cell Biol*. 2011 **31**:1201. [PMID: 21245379]
[19] Carrà G *et al. Cell Mol Life Sci*. 2020 **77**:4449. [PMID: 32322927]
[20] Webster GA *et al. Mol Cell Biol*. 1999 **19**:3485. [PMID: 10207072]
[21] Saeed M, Curr Drug Metab. 2018;19(9):798-805. [PMID: 29512446]
[22] Garcia PV *et al. BMC Cancer*. 2016 **16**:422. [PMID: 27389279]
[23] Gudkov AV *et al. Cold Spring Harb Perspect Med*. 2016 **6**:a026161. [PMID: 27549311]
[24] Kawasaki T *et al. Front Immunol*. 2014 **5**:461. [PMID: 25309543]
[25] Hori M *et al. Circ Res*. 2008 **102**:137. [PMID: 18239139]
[26] Anthoney N *et al. Development*. 2018 **145**:dev156018. [PMID: 29695493]
[27] Lim *KH et al. Cold Spring Harb Perspect Biol*. 2013 **5**:a011247. [PMID: 23284045]
[28] Zhang Y *et al. Infect Immun*. 2003 **71**:1513. [PMID: 12595470]
[29] Krysko DV et al. *Cell Death Differ*. 2011 **18**:1316. [PMID: 21311566]
[30] González-Reyes S *et al. Cancer Immunol Immunother*. 2011 **60**:217. [PMID: 20978888]
[31] Ioannou S *et al. Mediators Inflamm.* 2010 **2010**:581837. [PMID: 20871832]

Edited by P Kangueane
Citation: Alam *et al.* Bioinformation 17(9): 784-789 (2021)