Computational screening of phytochemicals against survivin protein: A potent target for cancer

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Abstract: Survivin (IAP proteins) is considered as a significant target for anticancer drug research owing to its upregulation in tumor cells to mediate resistance to apoptotic stimulus. The current study aimed to investigate phytochemicals as inhibitors of survivin with caspases to reactivate the functioning of caspases through molecular docking. The compounds namely 2(R), 4(R)-dihydroxypyrrolidine, 4-hydroxy-2-(4-methoxyphenyl)-1,1-dioxo-3,4-dihydrothieno[3,2-e]thiazine-6-sulfonamide, 2,3-Diketo-L-gulonic acid, (3-hydroxy-2-octadeca-9,12-dienoyloxypropyl) octadecanoate, 2-[[4-[[4-[(4-formamido-1-methylimidazole-2-carbonyl)amino]-1-methylimidazole-2-carbonyl]amino]-1-methylimidazole-2-carbonyl]amino]ethyl-dimethylazanium, Picolinic acid and (2-Hydroxy-5-nitrophenyl) dihydrogen phosphate successfully bind inside the pocket of survivin. ADMETsar was used to evaluate the anticancer potential of selected compounds. These compounds can be proposed as effective inhibitors, disrupting the survivin-caspases interaction and reactivating the caspases function of apoptosis. The study might facilitate the development of cost-effective and natural drugs against cancer. However, further validation is essential for confirmation of its drug efficacy and bio-compatibility.

Keywords: Survivin, medicinal plants, anticancer drugs, computational drug design.

INTRODUCTION

According to World Health Organization (WHO), cancer represents the utmost health challenges globally. Cancer is leading cause of mortality which account for death of approximately 8.8 million people and in 2015, 14.1 million cases were diagnosed which are predicted to increase in the coming years (Torre *et al*., 2015). Cancer is ascribed to uncontrolled growth of cells which harbors metastatic potential to attack or spread to nearby parts. It is fostered via mutations in the genome which leads to functional modification in several classes of protein families including cell surface receptors, signal transducers, cytokines and transcription factor contributing complexity in its treatment (Begley and Ellis, 2012, Hanahan and Weinberg, 2011). In 2013, oncology represented top ranked therapeutic class globally amounting to $73 billion (Bach, 2014).

There are different mechanisms behind cancer, one of these is inhibition of apoptosis (programmed cell death). Apoptosis can significantly slowdown carcinogenesis and thus hold great importance in cancer therapy. Repression of apoptosis has been reported in a number of cancers such as liver, breast and lung cancers (Wong 2011, Fesik 2005). Currently, two pathways of apoptosis are known: intrinsic and extrinsic pathways (Zhang and Zhang, 2015). Both apoptotic pathways are controlled by caspase proteins, such as executioner caspases (caspases-3, 6 and 7) and initiator caspases (caspase-8 and 9) (Fulda and Debatin, 2006). Apoptosis is established by cytochrome c (apoptotic factor), which activates caspase-3 and caspase-7 by binding to cardiolipin in inner membrane of mitochondria (Ott *et al*., 2002). The mitochondrial pathway is started by Bax/Bcl-2 pathway activation, leading to unleash of cytochrome c and apoptosis inducing factor (AIF) in cytoplasm from mitochondrial intermembrane. Cytochrome c activates caspase-3 by forming cytochrome c /Apaf-1/caspase-9 complex. Caspase-3 breaks cytoskeletal proteins and DNA. CAD (Caspase-activated DNase) and ICAD (inhibitor of CAD) start fragmentation of DNA (Jaiswal *et al*., 2015).

Caspase-3 and caspase-7 are also activated by caspase-9 and after activation these are responsible for destruction of cells (Brentnall *et al*., 2013). Hence, cell death activation can be started through binding of ligand (TNF, FasL) to death receptor or by mitochondrial signaling (Jaiswal *et al*., 2015). Overexpression of survivin inhibits apoptosis through caspase dependent and independent pathways (Small *et al*., 2010). Survivin is the tiniest entity of the blocker of apoptosis protein family, which has significant contribution in regulation of cell cycle and inhibition of programmed cell death by hindering caspase

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activation (Chen *et al*., 2016). Expression of survivin has been testified in 80 percent of malignancies making it as a strong biomarker of metastatic tumor (Mishra and Singh, 2018). Survivin is a member of IAP (inhibitor of apoptosis) gene family and has a molecular weight of 16.5-kDa (Altieri, 2001). IAP molecules are defined by presence of a ~70 amino acids zinc-finger fold, baculovirus IAP repeat (BIR) (Deveraux and Reed, 1999). IAPs also include a RING finger fold, a nucleotide binding P-loop motif, a ubiquitin-conjugating domain and a caspase-recruitment domain (CARD) (Deveraux and Reed, 1999). Survivin is smallest member of IAPs and contains only one of the N-terminal BIR domains; and an alpha-helix substitutes RING finger domain (Ambrosini *et al*., 1997). Survivin plays a dual function in cell division, regulation of cell cycle in G2/M phase and repression of apoptosis by blocking activation of caspase-3 and 7 (Knutsen *et al*., 2004, Wheatley and McNeish, 2005). Apoptosis blocking function of survivin is defined by presence of BIR domain (Ambrosini *et al*., 1997). As survivin lacks CARD motif, it does not directly suppress caspases. It interacts with adapter molecules i.e X-Linked IAP (XIAP). Survivin increases stability of XIAP by interacting with it (Sun *et al*., 2005). In this way, inhibitory activity of XIAP increases due to which caspase-9 mediated cell death is suppressed (Dohi *et al*., 2004). Interestingly, reports show contradiction on interaction between caspases and survivin. A few of them shows that survivin suppresses caspase-3, caspase-7 and caspase-9 by binding with them, whereas others are failed to explain direct effect on these proteases (Chandele *et al*., 2004). Survivin co-immunoprecipitated with active caspase-3 and 7, but inactive caspases did not co-immunoprecipitated with survivin(Wright *et al*., 2000, Song *et al*., 2003). The interaction between survivin and caspases disintegrates the caspase cascade and caspase mediated cleavage, resulting in decreased apoptosis (Tamm *et al*., 1998). Survivin also inhibits cytochrome-c and caspase-8-induced cleavage activity (Tamm *et al*., 1998). A study shows that survivin interacts with caspase-3, 7 and 9 when its Thr34 is phosphorylated by CDC2 (Singh *et al*., 2013). Studies indicate that a mutation of survivin can release cytochrome c from mitochondria and leads to apoptosis (Liu *et al*., 2004). Furthermore, p53 expression can be regulated by survivin. Survivin, in a dose-dependent manner, blocked p53-dependent apoptosis (Mirza *et al*., 2002), suggesting that p53-dependent apoptotic pathway is regulated by survivin. Moreover, survivin modifies p53 in degradation by MDM2/caspase-3 complex (Wang *et al*., 2004). Further studies indicated that survivin can lead to degradation of p53 if it inhibits the MDM2 cleavage, and ultimately cells with overexpression of survivin have decreased level of p53 (Wang *et al*., 2004).

In comparison with orthodox approaches of drug screening which include High Throughput Screening (HTS), newly simulated and computer based High Throughput Screening has revolutionized the identification of time and cost efficient novel drugs (Tahir Ul Qamar *et al*., 2019). In the current study, phytochemicals are used to design an artificial drug against survivin which suppresses survivin over expression and helps caspases to perform their normal function, leading to programmed cell death (apoptosis). The phytochemicals (secondary metabolites) found in medicinal plants have expressive anticancer potential due to their nutraceutical properties (Gull *et al*., 2015, Muhammad *et al*., 2015, Sahib *et al*., 2013). The consumption of phytomedicines increases due to their structural diversity, availability, exhibition of multiple target activities and negligible side effects (Sahib *et al*., 2013, Ahmed *et al*., 2014, Ashfaq *et al*., 2013). With the help of computer-aided drug designing tools the detection of therapeutic agents has become a reliable process (Riaz *et al*., 2017). In this respect, ligand docking with a 3D structure of survivin proves a consequential method in designing novel anticancer compounds. A library of about 8,000 phytochemicals have been screened against survivin to stop survivin-caspases interaction by using in-silico techniques. The experiential was to target hotspot residues that bind with caspases. The screened inhibitors can bind to hydrophobic cleft of survivin to stop caspase binding, which results in normal regulation of apoptosis. The results of these studies support the efficiency of anticancer phytomedicines and provoke its development (Dai *et al*., 2016). The guesstimated phytochemicals do not have side effects and toxicity in host cells (Kinghorn *et al*., 2009). These phytochemicals have ability to stop survivin-caspases interactions, with minute side effects. Disturbance of biological pathways has not been reported for suppression of survivin-caspases interactions with the use of phytochemicals (Kinghorn *et al*., 2009, Li *et al*., 2012).

MATERIALS AND METHODS

Structure retrieval and optimization

The 3D structure of survivin protein was retrieved from protein data bank (PDB) using PDB ID:1F3H. The retrieved structure was optimized removing ligand and solvent residues, 3D protonation (Labute, 2007) and energy minimization using Molecular Operating Environment (MOE) (2013). The structure was further minimized. This minimizes structure was handed-down as receptor for docking analysis (Ul Qamar *et al*., 2014).

Ligand library preparation

About 8,000 phytochemicals were retrieved from PubChem (Bolton *et al*., 2008), MPD3 (Mumtaz *et al*., 2017) and MAPS database (Ashfaq *et al*., 2013) and a ready-to-dock library was prepared. To scan the inhibitors, docking have been performed against survivin by using MOE software packages (Roy and Luck, 2007).

Table 1: Interaction detail of top seven bioactive phytochemicals in the proposed site of surviving protein

S no	Pub Chem ID	Chemical name	Docking score	RMSD value	Receptor	Interaction
1	1472	2(R), 4(R)-dihydroxypyrrolidine	-13.8575	1.3594	Lys15 Lys91 Asp16	H-donor H-acceptor H-acceptor
2	1612	4-hydroxy-2-(4-methoxyphenyl)-1,1-dioxo-3,4-dihydrothieno[3,2-e]thiazine-6-sulfonamide	-13.1252	0.9888	Lys15 Arg18 Phe93	H-donor H-pi H-donor
3	18	2,3-Diketo-L-gulonic acid	-12.3876	1.0112	Lys15 Phe93	H-donor H-donor
4	1. 1399	2. (3-hydroxy-2-octadeca-9,12-dienoyloxypropyl) octadecanoate	-11.9650	1.0979	Lys91 Gln92 Arg18	H-acceptor H-acceptor H-donor
5	1264	2-[[4-[[4-[(4-formamido-1-methylimidazole-2-carbonyl)amino]-1-methylimidazole-2-carbonyl]amino]-1-methylimidazole-2-carbonyl]amino]ethyl-dimethylazanium	-11.4654	0.9420	Lys91 Gln92	H-acceptor H-donor
6	1018	Picolinic acid	-10.9966	1.1933	Lys91 Phe93 Phe86	H-acceptor H-donor H-acceptor
7	1019	(2-Hydroxy-5-nitrophenyl) dihydrogen phosph ate	-10.7597	0.8193	Asp16 Lys15 Phe13	H-acceptor H-donor H-acceptor

Table 2: Results of compounds examined for Lipinski rule

Compound	Molecular weight (g/mol)	Number of HBA	Number of HBD	MLogP
Lipinski's rule of five	<500	<10	<5	<5
2(R), 4(R)-dihydroxypyrrolidine	478.45	5	5	0.47
4-hydroxy-2-(4-methoxyphenyl)-1,1-dioxo-3,4-dihydrothieno[3,2-e]thiazine-6-sulfonamide	380.35	9	2	3.66
2,3-Diketo-L-gulonic acid	315.37	7	4	0.99
(3-hydroxy-2-octadeca-9,12-dienoyloxypropyl) octadecanoate	346.33	5	1	-2.25
2-[[4-[[4-[(4-formamido-1-methylimidazole-2-carbonyl)amino]-1-methylimidazole-2-carbonyl]amino]-1-methylimidazole-2-carbonyl]amino]ethyl-dimethylazanium	332.44	7	5	2.35
3. Picolinic acid	299.29	3	1	-3.09
(2-Hydroxy-5-nitrophenyl) dihydrogen phosphate	332.26	7	3	-1.48

Table 3: ADMET profiling enlisting absorption, metabolism and toxicity related drug like parameters of candidate compounds

A. ADMET Profiling							
Compounds	2(R), 4(R)-dihydroxypyrrolidine	4-hydroxy-2-(4-methoxyphenyl)-1,1-dioxo-3,4-dihydrothieno[3, 2-e]thiazine-6-sulfonamide	2,3-Diketo-L-gulonic acid	(3-hydroxy-2-octadeca-9,12-dienoyloxypropyl) octadecanoate	2-[[4-[[4-[(4-formamido-1-methylimidazole-2-carbonyl)amino]-1-methylimidazole-2-carbonyl]amino]-1-methylimidazole-2-carbonyl]amino]ethyl-dimethylazanium	Picolinic acid	(2-Hydroxy-5-nitrophenyl) dihydrogen phosphate
A. Absorption							
Blood-Brain Barrier	No	No	No	No	No	No	High
Gastro- Intestinal Absorption	High	Low	Low	Low	High	Low	High
P-glycoprotein substrate	No	No	Yes	Yes	No	Yes	No
B. Metabolism							
CYP450 1A2 Inhibitor	No	No	No	No	No	No	No
CYP450 2C9 Inhibitor	No	No	No	No	No	No	No
CYP450 2D6 Inhibitor	No	No	Yes	No	Yes	No	No
CYP450 2C19 Inhibitor	No	No	Yes	No	No	No	No
CYP450 3A4 Inhibitor	No	No	No	No	Yes	No	No

Determination of hotspot residues

All residues which participate in the interaction of Survivin have been recognized and was selected using sie finder tool of MOE package.

Molecular docking

Ready-to-dock library of phytochemicals was docked with interacting residues of survivin by using docking algorithm of MOE software. Aicar (PubChem ID: 46780289) one of the inhibitors of survivin (Xiao and Li, 2015), shown in table 1, was also test-docked against survivin as reference ligand. Following were the parameters set for docking: placement: triangle matcher; re-scoring: London dG; retain: 10; refinement: Forcefield; re-scoring 2: London dG and retain 10. The MOE program validates accurate conformation of ligand to get minimum energy structure. After docking, phytochemicals with best and top conformation were determined on the basis of S-score and RMSD value.

The LigX tool of MOE was used to analyze the 2D plots of receptor ligand interactions that enable clear view of receptor ligand interaction of the best docked complexes.

In silico analysis of drug likeness and ADMET properties

The best docking scoring phytochemical was then subjected to further selection on the basis of Lipinski's rule of five (Ro5),(Lipinski, 2004)and compounds without any Ro5 violations were eliminated. This was simply done by Molinspiration server (Jarrahpour *et al*., 2012) for calculation of their physicochemical properties. In order to evaluate drug like characteristics the candidates were subjected to SwissADME software (Daina *et al*., 2017). The calculation of ADMET properties i.e. Absorption, Distribution, Metabolism, Excretion, and Toxicity are an important indication of drug candidate's behavior, fate and level of toxicity in human body. It gives probability of candidate's ability to pass through the Blood-brain barrier, its absorption in intestines, metabolism, distribution at subcellular level and most importantly the level of harm it can cause in body(Lin *et al*., 2003).

RESULTS

Database screening and docking study

The 3D structure of survivin was retrieved from Protein Data Bank by PDB ID: 1F3H, which had a resolution of 2.58 Å (Berman *et al*., 2000). This structure was optimized to find the antagonist that could interfere with the interaction and does not allow survivin to bind with caspases. Docking was performed by using ready-to-dock library of phytochemicals. All the residues participating in the reaction of survivin with other proteins or ligands were found with the help of MOE site finder tool. The library of Phytochemical was docked against the survivin protein and docked compounds were ranked on the basis of stringent filter that accounts four factors, maximum occupancy of binding pocket with minimum Gibbs free energy, strength of hydrogen bonding and other potential non-covalent interaction. Of 8000 docked molecules, seven top ranking docking poses were selected. The hit compounds were selected based on maximum binding sites occupied by ligand, minimum S-score and lower RMSD values. These candidate compounds exhibited their minimum binding energy in the range of -13.8575 Kcal/mol to -10.7597 Kcal/mol.

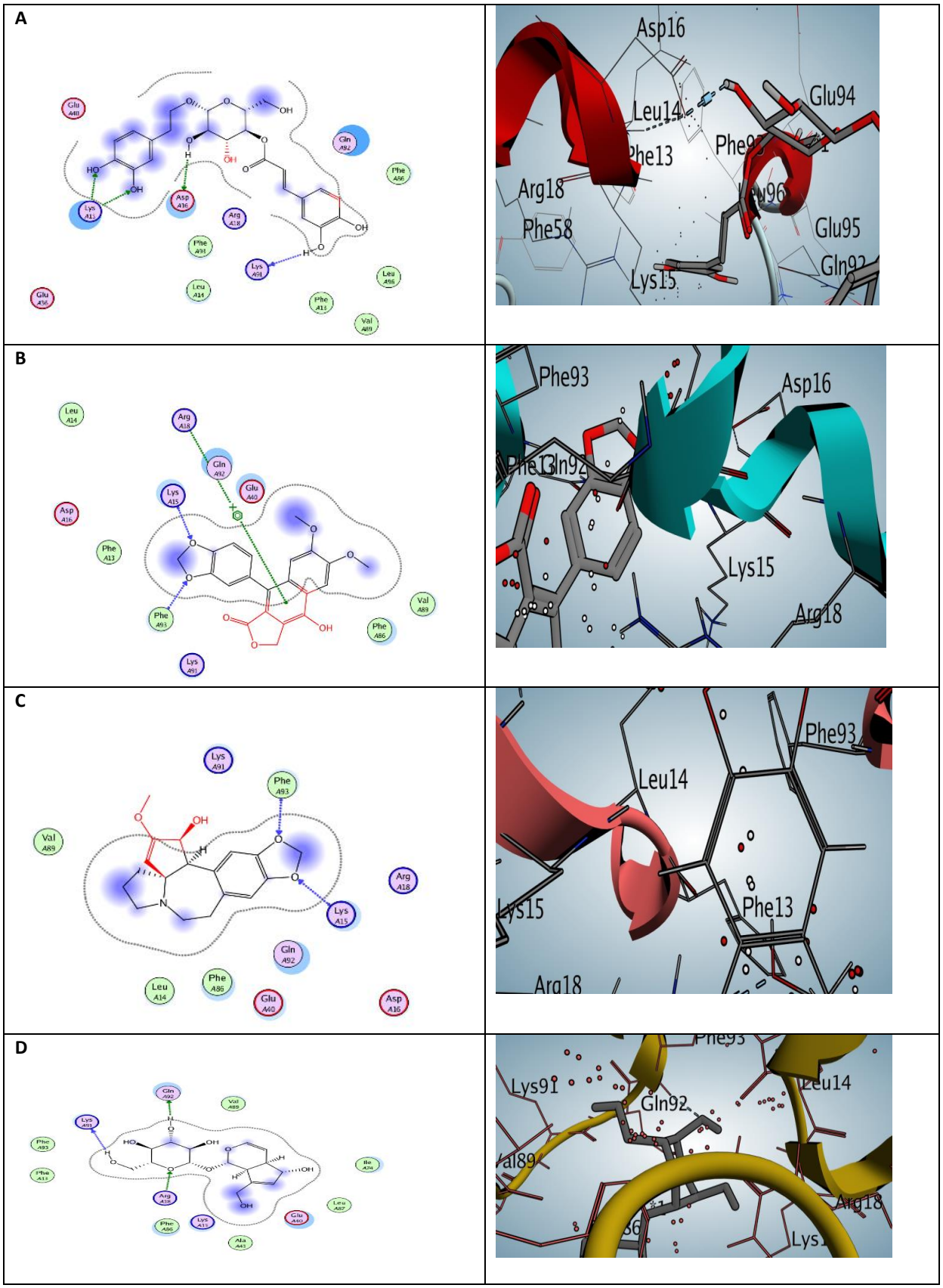
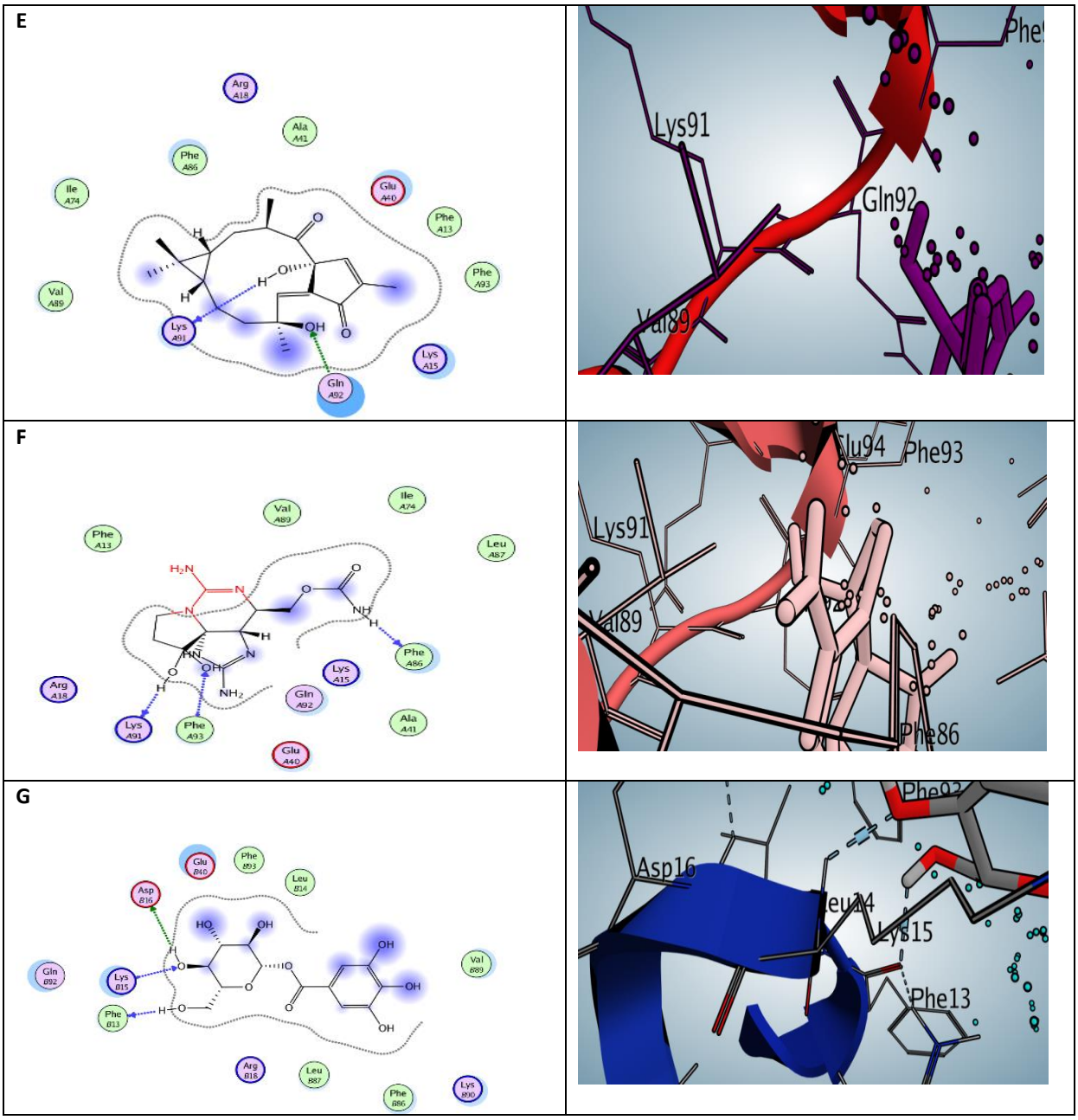


Fig. 1A: Docked 2(R), 4(R)-dihydroxypyrrolidinein complex with survivin; side chains atoms of Lys15, Lys91 and Asp16 making hydrogen bonds, shown in green line. Docked pose of compound highlighting the most active residues of protein's binding pocket is shown



B: Docked 4-hydroxy-2-(4-methoxyphenyl)-1,1-dioxo-3,4-dihydrothieno[3,2-e]thiazine-6-sulfonamidein complex with survivin; side chains atoms of the residues Lys15and Phe93are making hydrogen bonds and arene-cation interaction with Arg18, shown in green line. Docked pose of compound highlighting the most active residues of protein's binding pocket is shown at right.

C: Docked 2,3-Diketo-L-gulonic acid in complex with survivin; side chains atoms of Lys15 and Phe93 are making hydrogen bonds, shown in green line. Docked pose of compound highlighting the most active residues of protein's binding pocket is shown at right.

D: Docked (3-hydroxy-2-octadeca-9,12-dienoyloxypropyl) octadecanoate in complex with survivin; side chains atoms of Lys91, Gln92 and Arg18are making hydrogen bonds, shown in green line. Docked pose of compound highlighting the most active residues of protein's binding pocket is shown at right.

E: Docked 2-[[4-[[4-[(4-formamido-1-methylimidazole-2-carbonyl)amino]-1-methylimidazole-2-carbonyl]amino]-1-methylimidazole-2-carbonyl]amino]ethyl-dimethylazaniumin complex with survivin; side chains atoms Lys91 and Gln92, are making hydrogen bond shown in green line. Docked pose of compound highlighting the most active residues of protein's binding pocket is shown at right.

F: Docked Picolinic acid in complex with survivin; side chains atoms of Lys91, Phe93 and Phe86 are involved in hydrogen bond interaction, shown in green line. Docked pose of compound highlighting the most active residues of protein's binding pocket is shown at right.

G: Docked (2-Hydroxy-5-nitrophenyl) dihydrogen phosphate in complex with survivin; side chains atoms of Asp16, Lys15 and Phe13 are involved in hydrogen bond interaction, shown in green line. Docked pose of compound highlighting the most active residues of protein's binding pocket is shown at right.

However, for all the selected binding sites of the survivin protein, 2(R), 4(R)-dihydroxypyrrolidine was ranked at the top as it exhibited maximum binding score and binding affinity. Most of the phytochemicals i.e., four out of top seven tend to exhibit strong binding affinity toward amino acid Lys91and Lys15 suggesting that these are most active residues. These are followed by Phe93and Gln92 which exhibited interaction in selected three and two compounds respectively (fig. 1).

Absorption, distribution, metabolism, excretion (ADME) properties and toxicity scan

Molinspiration server was used to predict the drug likeliness of proposed survivin inhibitors using ADMET based drug scan. The selected candidate showed zero violations to the Lipinski's rule of five and acceptable drug-like properties, i.e. molecular weight (table 2). All the candidate compounds were subjected to Swiss ADME to assess them for their drug like properties, server in order to further validate the potential of drug likeliness (table 3).

DISCUSSION

In silico analysis has revolutionized drug designing by efficiently decreasing the hustle and total expenditure demanded by the conventional drug designing procedure. It has successfully cut short the resources going in Level I of drug designing i.e. Drug Discovery. With the advent of efficient bioinformatics databases, tools and software; new potential drugs and their targets are being discovered and published in great numbers. In silico compound libraries are available due to advancements in chemoinformatics. These compounds can be screened for their properties and drug-likeness owing to the modern computational methods (Terstappen and Reggiani, 2001).

In this study, we screened novel multi-target drug like compounds of plant origin and with desired ADME characteristics. Aiming that goal, *in silico* structure based drug design approach was designed to identify inhibitors which leads toward seven potent common phytochemicals including 2(R), 4(R)-dihydroxypyrrolidine, 4-hydroxy-2-(4-methoxyphenyl)-1,1-dioxo-3,4-dihydrothieno[3,2-e] thiazine-6-sulfonamide, 2,3-Diketo-L-gulonic acid, (3-hydroxy-2-octadeca-9,12-dienoyloxypropyl) octadeca-noate, 2-[[4-[[4-[(4-formamido-1-methylimidazole-2-carbonyl)amino]-1-methylimidazole-2-carbonyl] amino]-1-methylimidazole-2carbonyl] amino]ethyl-dimethyla-zanium, Picolinic acid and (2-Hydroxy-5-nitro-phenyl) dihydrogen phosphate. These phyto-chemicals were screened based on their binding affinity and score. The docking study established the residues that play the most important roles on the binding affinity, namely: Lys91 and Lys15 >Phe93 >Gln92.

Survivin is associated with dual function as it concomitantly operational in both cell division and apoptosis inhibition. It is upregulated in human neoplasm and down regulated or undetectable in differentiated normal tissues (Pennati *et al*., 2007). The significant up regulation of survivin is responsible for tumor progression, low survival rate, drug resistance, tumour recurrence as well as poor prognosis. All this fostered the need of developing its inhibitors as an anti-cancer agent (Fukuda and Pelus, 2006). The agents including small-molecule inhibitors, molecular antagonists, antisense inhibitor, transcriptional repressor and vaccine based therapies is appropriate for inhibitor of survivin (Kelly *et al*., 2011).

Several studies aimed to discover potent inhibitor of survivin protein. In one study 115 Plant compound from NPACT database were docked against Survivin protein using iGEMDock2.1 which revealed Remangilones A as potent inhibitor of protein survivin with total energy of -121.465kcal mol-1(SD Amanulla *et al*., 2017). The dried leaves extract of Physenamadagascarienis is a potential source of Remangilones A which is kind of dinortriterpenes that demonstrated to exhibit cytotoxic effect against MDA-MB-435 and MDA-MB-231 breast cancer cells mediated by apoptosis (Deng *et al*., 1999).

Eram *et al*. (2017) employed virtual screening approach to screen marine compounds inhibiting survivin which identified that analog (AP 4) of Aplysin, is a promising candidate as it showed binding energy of -8.75 kcal/mol which proposed it to be a potential inhibitor of survivin protein. The finding was comparable to its known inhibitor Celecoxib having binding energy of -6.65 kcal/mol and Ki 13.43μM (Shakeel *et al*., 2017).

Another study reported that plant-derived compounds namely coclaurine, coreximine and synephrine from Annona muricata showed strong energy based affinity -9.95 kcal/mol and -8.23 kcal/mol with Bcl-2 and survivin respectively by the ranking of poses generated by A Score scoring function of Argus Lab,important proteins in cell cycle regulation (Muthu and Durairaj, 2016).

The similar findings were reported by Kalim and his coworkers who proved that that Quercetin exhibited promising binding efficacy with -7.90 kcal/mol and chemo preventive potential against survivin(Khan *et al*., 2015). D Afriza *et al*. (2018) studied potential of phytochemical compounds dentatin, nordentatin, and quercetin and proposed that these exhibited hydrophobic interactions in common with three residues namely Phe86, Phe93, Ile74. Moreover dentatin were involved in electrostatic interactions survivin (Lys78). Therefore targeting survivin in order to hamper its apoptotic activities is considered as a most effective strategy for inhibiting cancer cell growth (Afriza *et al*., 2018). Furthermore, an alkaloid Piperine has been reported to be most promising adjuvant at increasing the efficacy of tumor necrosis factor-related apoptosis-inducing ligand

(TRAIL)-mediated therapies for targeting triple-negative breast cancer (TNBC) cells both *in vivo* and *in vitro* modulated through inhibition of Survivin. The moleculer docking studies proposed effective binding of Piperine and some of its derivatives into to BIR domain of Survivin that might result in dissociation of Smac/ DIABLO freely in the cytosol which render it available for interaction with inhibitors of apoptosis thereby triggering caspase mediated apoptosis (Sattarinezhad *et al*., 2015).

Our study identified seven inhibitors with strong potential of drug lead that may be one therapeutic inhibitor of survivin by efficiently targeting and inhibiting the apoptosis. Therefore, our findings regarding bioactivity of2(R), 4(R)-dihydroxypyrrolidine, 4-hydroxy-2-(4-methoxyphenyl)-1,1-dioxo-3,4-dihydroth-ieno[3,2-e]thia-zine-6-sulfonamide, 2,3-Diketo-L-gulonic acid, (3-hydro-xy-2- octadeca-9,12- dienoyloxypropyl) octadecanoate, 2-[[4-[[4-[(4-formamido-1-methylimidazole-2-carbonyl) amino]-1-methylimidazole-2-carbonyl]amino]-1-methyli midazole-2-carbonyl]amino] ethyl-dimethylazanium, Picolinic acid and (2-Hydroxy-5-nitrophenyl) dihydrogen phosphate warrant further experimental work for structure based leads optimization.

CONCLUSION

In the current study phytochemicals including 2(R), 4(R)-dihydroxypyrrolidine, 4-hydroxy-2-(4-methoxyphenyl)-1,1-dioxo-3,4-dihydrothieno[3,2-e]thiazine-6-sulfona-mide, 2,3-Diketo-L-gulonic acid, (3-hydroxy-2-octadeca-9,12-dienoyloxypropyl) octadecanoate, 2-[[4-[[4-[(4-formamido-1-methylimidazole-2-carbonyl)amino]-1-me-thylimidazole-2-carbonyl]amino]-1-methylimidazo le-2-carbonyl]amino]ethyl-dimethylazanium, Picolinic acid and (2-Hydroxy-5-nitrophenyl) dihydrogen phosphateare identified as the potential phytochemicals that shows strong binding capability with survivin protein and shows all of the drug-like properties. The results of our present study can be useful for the design and development of novel compounds having better inhibitory activity against survivin protein. Further *in vitro* and *in vivo* studies are highly advised to check for the efficacy of this study.

REFERENCES

Chemical Computing Group Inc. MOE: Molecular Operating Enviornment (MOE). Montreal, QC, Chemical Computing Group Inc., Canada.

Afriza D, Suriyah W & Ichwan S (2018). *In silico* analysis of molecular interactions between the anti-apoptotic protein survivin and dentatin, nordentatin, and quercetin. Journal of Physics: Conference Series. IOP Publishing, 032001.

Ahmed B, Ashfaq UA, Ul Qamar MT and Ahmad M (2014). Anticancer potential of phytochemicals against breast cancer: Molecular docking and simulation approach. *Bangladesh J. Pharmacol.*, **9**: 545-550.

Altieri DC (2001). The molecular basis and potential role of survivin in cancer diagnosis and therapy. *Trends Mol. Med.*, **7**: 542-547.

Ambrosini G, Adida C and Altieri DC (1997). A novel anti-apoptosis gene, survivin, expressed in cancer and lymphoma. *Nature Medicine*, **3**: 917-921.

Ashfaq UA, Mumtaz A, Ul Qamar T and Fatima T (2013). MAPS Database: Medicinal plant activities, phytochemical and structural database. *Bioinformation*, **9**: 993.

Bach PB (2014). Indication-specific pricing for cancer drugs. *Jama*, **312**: 1629-1630.

Begley CG and Ellis LM (2012). Drug development: Raise standards for preclinical cancer research. *Nature*, **483**: 531.

Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN and Bourne PE (2000). The protein data bank. *Nucleic acids research*, **28**: 235-242.

Bolton EE, Wang Y, Thiessen PA and Bryant SH (2008). PubChem: integrated platform of small molecules and biological activities. Annual Reports in Computational Chemistry. Elsevier.

Brentnall M, Rodriguez-Menocal L, De Guevara RL, Cepero E and Boise LH (2013). Caspase-9, caspase-3 and caspase-7 have distinct roles during intrinsic apoptosis. *BMC Cell Biology*, **14**: 32.

Chandele A, Prasad V, Jagtap JC, Shukla R and Shastry PR (2004). Upregulation of survivin in G2/M cells and inhibition of caspase 9 activity enhances resistance in staurosporine-induced apoptosis. *Neoplasia*, **6**: 29-40.

Chen X, Duan N, Zhang C and Zhang W 2016. Survivin and Tumorigenesis: Molecular Mechanisms and Therapeutic Strategies. *J. Cancer*, **7**: 314-323.

Dai SX, Li WX, Han FF, Guo YC, Zheng JJ, Liu JQ, Wang Q, Gao YD, Li GH and Huang JF (2016). In silico identification of anti-cancer compounds and plants from traditional Chinese medicine database. *Scientific Reports*, **6**: 25462.

Daina A, Michielin O and Zoete V 2017. Swiss ADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *ScientificReports*, **7**: 42717.

Deng Y, Jiang TY, Sheng S, Tianasoa-Ramamonjy M & Snyder JK (1999). Remangilones AC, New Cytotoxic Triterpenes from Physena m adagascariensis. *J. Nat. Prod.*, **62**: 471-476.

Deveraux QL and Reed JC (1999). IAP family proteins suppressors of apoptosis. *Genes & Development*, **13**: 239-252.

Dohi T, Okada K, Xia F, Wilford CE, Samuel T, Welsh K, Marusawa H, Zou H, Armstrong R and Matsuzawa SI 2004. An IAP-IAP complex inhibits apoptosis. *J. Biol. Chem.*, **279**: 34087-34090.

Fesik SW (2005). Promoting apoptosis as a strategy for cancer drug discovery. *Nature Reviews Cancer*, **5**: 876.

Fukuda S and Pelus LM (2006). Survivin, a cancer target with an emerging role in normal adult tissues. *Molecular Cancer Therapeutics*, **5**: 1087-1098.

Fulda S and Debatin KM 2006. Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy. *Oncogene*, **25**: 4798.

Gull T, Anwar F, Sultana B, Alcayde MAC and Nouman W (2015). Capparis species: A potential source of bioactives and high-value components: A review. *Industrial Crops and Products*, **67**: 81-96.

Hanahan D and Weinberg RA (2011). Hallmarks of cancer: The next generation. *Cell*, **144**: 646-674.

Jaiswal PK, Goel A and Mittal R (2015). Survivin: A molecular biomarker in cancer. *The Indian Journal of Medical Research*, **141**: 389.

Jarrahpour A, Fathi J, Mimouni M, Hadda TB, Sheikh J, Chohan Z and Parvez A (2012). Petra, Osiris and Molinspiration (POM) together as a successful support in drug design: Antibacterial activity and biopharmaceutical characterization of some azo Schiff bases. *Med. Chem. Res.*, **21**: 1984-1990.

Kelly RJ, Lopez-Chavez A, Citrin D, Janik JE and Morris JC (2011). Impacting tumor cell-fate by targeting the inhibitor of apoptosis protein survivin. *Molecular Cancer*, **10**: 35.

Khan M, Siddiqui M, Akhtar S, Ahmad K, Baig M and Osama K (2015). Screening of plant-derived natural compounds as potent chemotherapeutic agents against breast cancer: An in silico approach. *J. Chem. Pharm. Res.*, **7**: 519-526.

Kinghorn AD, Chin YW and Swanson SM (2009). Discovery of natural product anticancer agents from biodiverse organisms. *Current Opinion in Drug Discovery & Development*, **12**: 189.

Knutsen A, Adell G and Sun XF (2004). Survivin expression is an independent prognostic factor in rectal cancer patients with and without preoperative radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.*, **60**: 149-155.

Labute P (2007). Protonate 3D: Assignment of macromolecular protonation state and geometry. Chemical Computing Group Inc.

Li YJ, Kukita A, Watanabe T, Takano T, Qu P, Sanematsu K, Ninomiya Y and Kukita T (2012). Nordihydroguaiaretic acid inhibition of NFATc1 suppresses osteoclastogenesis and arthritis bone destruction in rats. *Laboratory Investigation*, **92**: 1777.

Lin J, Sahakian DC, De Morais S, Xu JJ, Polzer RJ and Winter SM (2003). The role of absorption, distribution, metabolism, excretion and toxicity in drug discovery. *Curr. Top. Med. Chem.*, **3**: 1125-1154.

Lipinski CA (2004). Lead-and drug-like compounds: the rule-of-five revolution. *Drug Discovery Today: Technologies*, **1**: 337-341.

Liu T, Brouha B and Grossman D (2004). Rapid induction of mitochondrial events and caspase-independent apoptosis in Survivin-targeted melanoma cells. *Oncogene*, **23**: 39.

Mirza A, Mcguirk M, Hockenberry TN, Wu Q, Ashar H, Black S, Wen SF, Wang L, Kirschmeier P and Bishop WR (2002). Human survivin is negatively regulated by wild-type p53 and participates in p53-dependent apoptotic pathway. *Oncogene*, **21**: 2613.

Mishra S and Singh S (2018). Identification of Inhibitors against Metastasis Protein "Survivin:" In silico Discovery Using Virtual Screening and Molecular Docking Studies. *Pharmacogn. Mag.*, **13**: S742-S748.

Muhammad G, Hussain Ma, Anwar F, Ashraf M and Gilani AH (2015). Alhagi: A plant genus rich in bioactives for pharmaceuticals. *Phytotherapy Research*, **29**: 1-13.

Mumtaz A, Ashfaq UA, Ul Qamar MT, Anwar F, Gulzar F, Ali MA, Saari N and Pervez MT (2017). MPD3: A useful medicinal plants database for drug designing. *Nat. Prod. Res.*, **31**: 1228-1236.

Muthu S and Durairaj B (2016). Molecular docking studies on interaction of Annona muricata compounds with antiapoptotic proteins Bcl-2 and survivin. *Sky. J. Biochem. Res*, **5**: 14-17.

Ott M, Robertson JD, Gogvadze V, Zhivotovsky B and Orrenius S (2002). Cytochrome c release from mitochondria proceeds by a two-step process. *Proc. Natl. Acad. Sci. USA*, **99**: 1259-1263.

Pennati M, Folini M and Zaffaroni N 2007. Targeting survivin in cancer therapy: Fulfilled promises and open questions. *Carcinogenesis*, **28**: 1133-1139.

Riaz M, Ashfaq UA, Qasim M, Yasmeen E, Ul Qamar M T and Anwar F (2017). Screening of medicinal plant phytochemicals as natural antagonists of p53-MDM2 interaction to reactivate p53 functioning. *Anti-cancer Drugs*, **28**: 1032-1038.

Roy U and Luck LA (2007). Molecular modeling of estrogen receptor using molecular operating environment. *Biochem. Mol. Biol. Educ.*, **35**: 238-243.

Sahib NG, Anwar F, Gilani AH, Hamid AA, Saari N and Alkharfy KM (2013). Coriander (*Coriandrum sativum* L.): A potential source of high-value components for functional foods and nutraceuticals: A review. *Phytotherapy Research*, **27**: 1439-1456.

Sattarinezhad E, Bordbar AK and Fani N (2015). Piperine derivatives as potential inhibitors of Survivin: an in silico molecular docking. *Computers in Biology and Medicine*, **63**: 219-227.

Sd Amanulla S, Veerakumar S and Ramanathan K (2017). Screening of potential plant compounds as survivin inhibitors and its anti-cancer efficacy by molecular docking. *Current Enzyme Inhibition*, **13**: 41-48.

Shakeel E, Akhtar S, Khan MKA, Lohani M, Arif JM and Siddiqui MH (2017). Molecular docking analysis of aplysin analogs targeting survivin protein. *Bioinformation*, **13**: 293.

Singh M, Chaudhry P, Fabi F and Asselin E (2013). Cisplatin-induced caspase activation mediates PTEN

cleavage in ovarian cancer cells: A potential mechanism of chemoresistance. *BMC Cancer,* **13**: 233.

Small S, Keerthivasan G, Huang Z, Gurbuxani S and Crispino JD (2010). Overexpression of survivin initiates hematologic malignancies *in vivo*. *Leukemia*, **24**: 1920.

Song Z, Yao X and Wu M (2003). Direct interaction between survivin and Smac is essential for the anti-apoptotic activity of survivin during Taxol-induced apoptosis. *J. Biol. Chem.*, **278**(25): 23130-23140.

Sun C, Nettesheim D, Liu Z & Olejniczak ET (2005). Solution structure of human survivin and its binding interface with Smac/Diablo. *Biochemistry*, **44**: 11-17.

Tahir Ul Qamar M, Maryam A, Muneer I, Xing F, Ashfaq UA, Khan FA, Anwar F, Geesi MH, Khalid RR, Rauf SA and Siddiqi AR (2019). Computational screening of medicinal plant phytochemicals to discover potent pan-serotype inhibitors against dengue virus. *Sci. Rep.*, **9**: 1433.

Tamm I, Wang Y, Sausville E, Scudiero DA, Vigna N, Oltersdorf T and Reed JC (1998). IAP-family protein survivin inhibits caspase activity and apoptosis induced by Fas (CD95), Bax, caspases, and anticancer drugs. *Cancer Research*, **58**: 5315-5320.

Terstappen GC and Reggiani A (2001). In silico research in drug discovery. *Trends in Pharmacological Sciences*, **22**: 23-26.

Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J & Jemal A (2015). Global cancer statistics, 2012. *CA Cancer J. Clin.*, **65**: 87-108.

Ul Qamar MT, Mumtaz A, Ashfaq UA, Adeel MM & Fatima T (2014). Potential of plant alkaloids as dengue ns3 protease inhibitors: Molecular docking and simulation approach. *Bangladesh J. Pharmacol.*, **9**: 262-267.

Wang Z, Fukuda S and Pelus LM (2004). Survivin regulates the p53 tumor suppressor gene family. *Oncogene*, **23**: 8146.

Wheatley SP and Mcneish IA (2005). Survivin: A protein with dual roles in mitosis and apoptosis. *International review of cytology*, **247**: 35-88.

WONG RS (2011). Apoptosis in cancer: From pathogenesis to treatment. *J. Exp. Clin. Cancer Res.*, **30**: 87.

Wright ME, Han DK and Hockenbery DM (2000). Caspase-3 and inhibitor of apoptosis protein (s) interactions in Saccharomyces cerevisiae and mammalian cells. *FEBS letters*, **481**: 13-18.

XIAO M and LI W (2015). Recent advances on small-molecule Survivin inhibitors. *Current Medicinal Chemistry*, **22**: 1136-1146.

Zhang C & Zhang F (2015). Iron homeostasis and tumorigenesis: molecular mechanisms and therapeutic opportunities. *Protein & Cell*, **6**: 88-100.