Journal of Applied Pharmaceutical Science Vol. 5 (11), pp. 073-078, November, 2015
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2015.501112
ISSN 2231-3354 

In silico analysis of indole-3-carbinol and its metabolite DIM as EGFR tyrosine kinase inhibitors in platinum resistant ovarian cancer vis a vis ADME/T property analysis

Raju Dash[1], S. M. Zahid Hosen[2*], Md. Rezaul Karim[3], Mohammad Shah Hafez Kabir[4], Mohammed Munawar Hossain[4], Md. Junaid[5], Ashekul Islam[6], Arkajyoti Paul[1], Mohammad Arfad Khan[1]

[1]Department of Pharmacy, BGC Trust University Bangladesh, Chittagong-4000, Bangladesh. [2] Pharmacology Research Division, BCSIR, Chittagong-4220, Bangladesh. [3] Institute of Food Science & Technology (IFST), BCSIR, Dhaka. [4]Department of Pharmacy, International Islamic University Chittagong, Chittagong-4203, Bangladesh. [5]Department of Pharmaceutical Sciences, North South University, Dhaka-1229, Bangladesh. [6]Department of Biochemistry and Molecular Biology, University of Chittagong, Chittagong-4331, Bangladesh.

ARTICLE INFO

Article history:
Received on: 24/08/2015
Revised on: 17/09/2015
Accepted on: 10/10/2015
Available online: 27/11/2015

Key words:
3, 3'-diindolylmethane, Indole-3-carbinol, Epidermal Growth Factor Receptor, Molecular simulation, SOM prediction.

ABSTRACT

Epidermal Growth Factor Receptor (EGFR) is one of the four members of the Human Epidermal Receptor (HER) family, which is deregulated and over expressed in platinum resistant ovarian cancer. Thus, targeting EGFR receptor along with platinum drugs is one of the major strategies to increase the platinum drug sensitivity. That's why, in this study, we aimed to investigate the inhibitory activity and binding site analysis of indole-3-carbinol and its active metabolite 3,3'-diindolylmethane by using molecular simulation studies, also metabolic profile had been investigated by SOM prediction. The 3,3'-diindolylmethane showed significant inhibitory activity and binding energy comparing to indole-3-carbinol, also it processed lower toxicity and will undergo aromatic hydroxylation due its high intrinsic activity and Fe accessibility. Though our research study supports previous reports of EGFR inhibition, further in vivo study is necessary for validation of toxicological and pharmacokinetic study. However, the current work tries to address most of the variables in the dynamic drug design process by *In silico* study in order to boost the potentiality of the selected molecule to serve as good leads in terms of optimum pharmacokinetic and toxicological attributes.

INTRODUCTION

Until recently, ovarian cancer is one of the most lethal of all gynecologic malignancies, causing more than about 140000 deaths each year worldwide (Jemal *et al.*, 2011). Most women with epithelial ovarian cancer (EOC) are diagnosed at advanced stages, where it is the fact that high mortality rate of this disease is caused by its poor prognosis (Slatnik and Duff, 2015). The clinical response rate is initially high and the platinum based compounds are standard first-line agents for ovarian cancer (Herzog, 2004). However, the ensuing reversion and recurring challenges of chemotherapeutic agents leads to the development of acquired chemoresistance, which is recurrent and closely linked to the poor survival associated with this cancer (Agarwal and Kaye, 2003; Rabik and Dolan, 2007). Therefore, developing novel and effective therapeutic strategies against ovarian cancer is urgently needed, and chemotherapy in combination with other inhibitors, is one of the standard chemotherapy standard initial management for ovarian cancer patients at advanced stages (Hennessy *et al.*, 2009; Bible *et al.*, 2012). Epidermal Growth Factor Receptor (EGFR) is one of the four members of the Human Epidermal Receptor (HER) family, which is over expressed in multiple malignancies, especially in ovarian cancer with poor prognosis (Bull Phelps *et al.*, 2008).

It is one of the tyrosine kinases that can be activated by extracellular ligands, which leads to receptor autophosphorylation and subsequent activation of downstream pathways involved in proliferation, survival, angiogenesis, and invasion (Scaltriti and Baselga, 2006; Lemmon and Schlessinger, 2010).

* *Corresponding Author*
S. M. Zahid Hosen, Pharmacology Research Division, BCSIR, Chittagong-4220, Bangladesh. Email: smzahidhosen@bcsir.gov.bd

The EGFR pathway is recurrently activated in cancer cell, and its targeted inhibition with a small molecule kinase inhibitor has been successful for lung, breast and ovarian cancer with EGFR mutations (Yarden and Sliwkowski, 2001; Cataldo *et al.,* 2011). 3,3'-diindolylmethane (DIM), an active metabolite of indole-3-carbinol, is present in cruciferous vegetables (Ciska *et al.,* 2009). Several studies have indicated an inverse relationship between intake of cruciferous vegetables and the risk of ovarian cancer and also concluded that DIM possesses chemopreventive and therapeutic properties (Rahman and Sarkar, 2005; Kandala and Srivastava, 2010).

Therefore, the present study was aimed to investigate the therapeutic properties of indole-3-carbinol and its metabolite DIM as EGFR tyrosine kinase inhibitor through various computational analyses, including molecular docking (Dash *et al.,* 2014; Dash *et al.,* 2015; Raju Dash *et al.,* 2015) and ADME and Toxicity analysis.

MATERIALS AND METHODS

Protein Preparation

Three dimensional crystal structure of epidermal growth factor receptor kinase domain (PDB id: 1M17) was downloaded in pdb format from the protein data bank (Berman *et al.,* 2000). After that, structure was prepared and refined using the Protein Preparation Wizard of Schrödinger-Maestro v9.4. Charges and bond orders were assigned, hydrogens were added to the heavy atoms, selenomethionines were converted to methionines, and all waters were deleted. Reorientation of certain hydroxyl and thiol groups, amide groups of asparagines, glutamines and imidazole ring of histidines, protonation states of histidines, aspartic acids, and glutamic acids was optimized at neutral pH. Using force field OPLS_2005, minimization was carried out setting maximum heavy atom RMSD to 0.30 Å.

Ligand Preparation

Compounds were retrieved from Pubchem databases, i.e. indole-3-carbinol (CID 3712) and 3, 3'-diindolylmethane (CID 3071). The 3D structures for these were built by using Ligprep2.5 in Schrödinger Suite 2013 with an OPLS_2005 force field. Their ionization states were generated at pH7.0±2.0 using Epik2.2 in Schrödinger Suite. Up to 32 possible stereoisomers per ligand were retained.

Receptor grid generation

Receptor grids were calculated for prepared proteins such that various ligand poses bind within the predicted active site during docking. In Glide, grids were generated keeping the default parameters of van der Waals scaling factor 1.00 and charge cutoff 0.25 subjected to OPLS 2001 force field.

A cubic box of specific dimensions centred around the centroid of the active site residues (Reference ligand active site) was generated for receptor. The bounding box was set to 14 Å × 14 Å × 14 Å for docking experiments.

Glide Standard Precision (SP) ligand docking

SP flexible ligand docking was carried out in Glide of Schrödinger-Maestro v9.4 (Friesner *et al.,* 2004; Friesner *et al.,* 2006) within which penalties were applied to non-cis/trans amide bonds. Van der Waals scaling factor and partial charge cutoff was selected to be 0.80 and 0.15, respectively for ligand atoms. Final scoring was performed on energy-minimized poses and displayed as Glide score. The best docked pose with lowest Glide score value was recorded for each ligand.

Prime MM-GBSA

Prime MM-GBSA approach was used to calculate ligand binding energies and ligand strain energies for a ligand and a single receptor. MM-GBSA is a method that combines OPLSAA molecular mechanics energies (EMM), an SGB solvation model for polar solvation (GSGB), and a non-polar solvation term (GNP) composed of the non-polar solvent accessible surface area and van der Waals interactions. Here, the Glide pose viewer file of the best conformation chosen was given as the source in Prime MM-GBSA simulation. The total free energy of binding:

$\Delta G_{bind} = G_{complex} - (G_{protein} + G_{ligand})$, where G = EMM + GSGB + GNP

ADME/T property analysis

Ligand based ADME/Toxicity prediction

The QikProp module of Schrodinger is a quick, accurate, easy-to-use absorption, distribution, metabolism, and excretion (ADME) prediction program design to produce certain descriptors related to ADME. It predicts both physicochemical significant descriptors and pharmacokinetically relevant properties. ADME properties determine drug-like activity of ligand molecules based on Lipinski's rule of five. ADME/T properties of the compound (DIM) was analysed using Qikprop 3.2 module (Natarajan *et al.,* 2015).

Structure-based P450 site of metabolism

The P450 Site of Metabolism (SOM) of selected compound was determined by 'induced fit docking' on CYP2D6 isoform using the 'P450 Site of Metabolism' module of Schrodinger Suite v9.3. For a given atom in a molecule to be a significant site of metabolism by a CYP450 isoform, it must have some degree of 'reactivity' in the absence of the enzyme and also be accessible to the reactive heme iron center. To address both these requirements, the 'P450 Site of Metabolism' workflow which combines induced-fit docking (IFD) for the determination of accessibility to the reactive center, with a rule-based approach to intrinsic reactivity, was used.

RESULTS

Molecular docking and binding energy analysis

In order to study the interaction of indole-3-carbinol and its active metabolite DIM with EGFR kinase, we performed Glide docking analysis by Schrodinger suite, where DIM processed

higher docking score than indole-3-carbinol, shown in Table 1. The negative and low value of free energy of binding demonstrates a strong favorable bond between EGFR kinase and DIM in most favourable conformations. Post docking analysis, shown in Figure 1 & 2, described the binding mode of indole-3-carbinol and DIM, in the active site of EGFR kinase domain. Though major residues like ASP831, THR830, MET742, PHE832, GLU738, LYS721, LEU764, THR766, ILE765, ALA719, ILE720, VAL702, LEU820 were found to be complimentary in both ligand's binding sites, significant differences in the hydrogen bonding were also observed. Here, hydrogen of hydroxyl group of indole-3-carbinol was seen to have hydrogen bonding with ASP831 residue, while hydrogen of amino group was involved with the same residue, in case of DIM. GLU 738 residue was also occupied with hydrogen of amino group indole-3-carbinole. Again, in order to describe the overall clarity of docking studies, we introduced Prime MM-GBSA (Adasme-Carreno *et al.*, 2014) approach to calculate ligand binding energies. As the MM-GBSA binding energies are approximate free energies of binding, a more negative value indicates stronger binding. In our study, highest binding energy was observed in DIM, comparing to indole-3-carbinol, indicating the accuracy of ligand protein binding (Table 1).

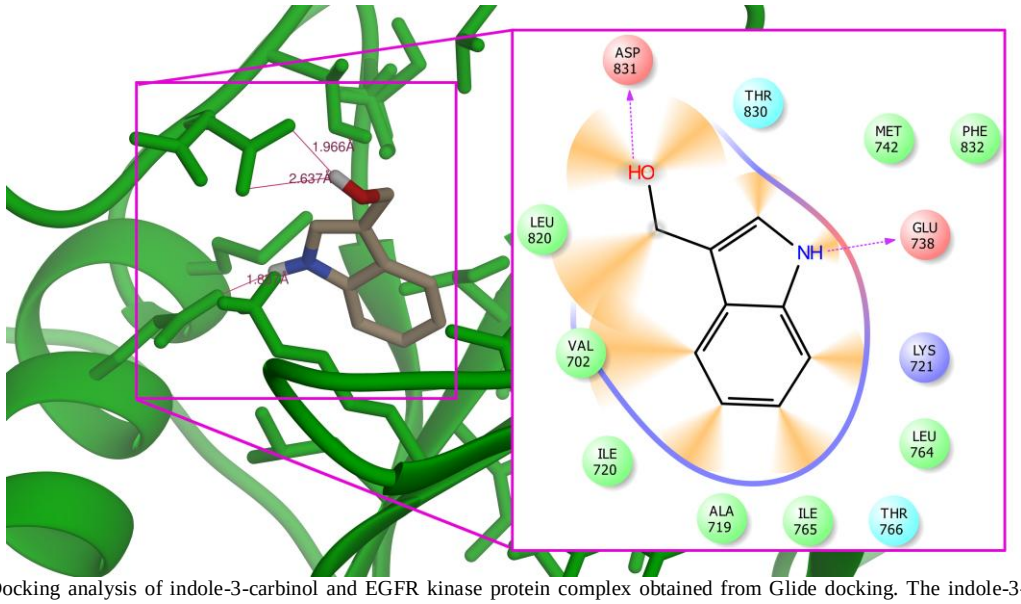

Fig. 1: Molecular Docking analysis of indole-3-carbinol and EGFR kinase protein complex obtained from Glide docking. The indole-3-carbinol molecule is shown as stick, protein as cartoon, and H-bonds as pink lines.

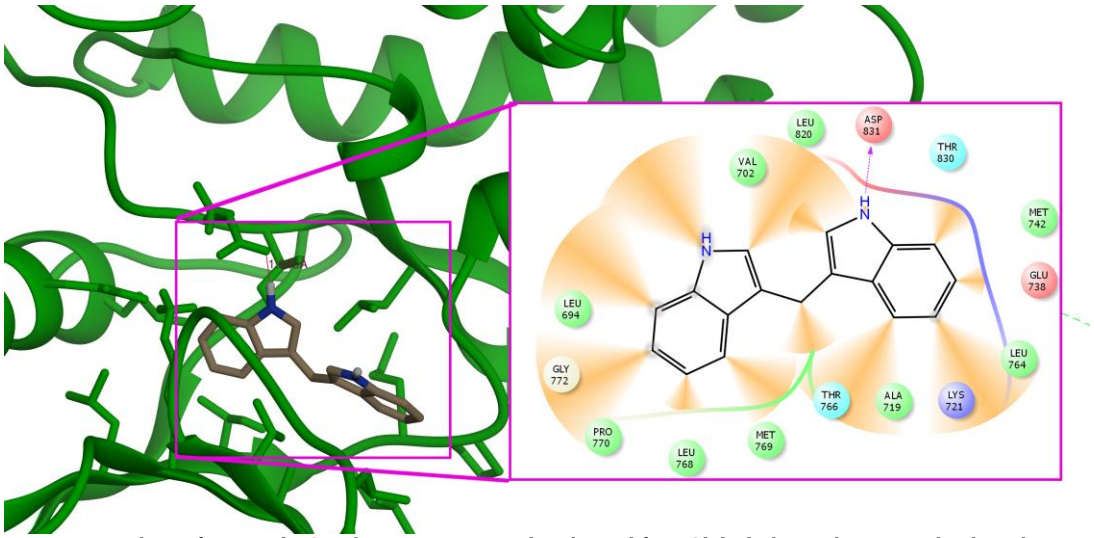

Fig. 2: Molecular interaction analysis of DIM and EGFR kinase protein complex obtained from Glide docking. The DIM molecule is shown as stick, protein as cartoon, and H-bonds as pink lines.

Table 1: Docking results of selected hits in kcal/mol.

Compound Name	ΔG_{bind}	Docking score	Glide energy	Glide ligand efficiency	Strain penalty	Glide Emodel
Indole-3 -carbinol	-32.46	-6.442	-27.542	-0.585	0	-39.026
3,3'-Diindolylmethane	-49.00	-6.875	-37.112	-0.361	0	-52.481

Table 2: ADME and drug likeness properties of the selected ligands by QikProp.

Name	MW[b]	HB donor[c]	HB acceptor[d]	SASA[e]	QP log HERG[f]	QP log S[g]	QP log Po/w[h]	% Human Oral Absorption[i]
3,3'-Diindolylmethane	246.311	2	0	489.494	-5.425	-4.364	4.215	100

[b]Molecular weight (acceptable range: <500).
[c]Hydrogen bond donor (acceptable range: ≤5).
[d]Hydrogen bond acceptor (acceptable range: ≤10).
[e]Total Solvent Accessible Surface Area in using a probe with a 1.4 radius (acceptable range: 300–1000).
[f]Predicted IC50 value for blockage of HERG K+ channels (concern: below −5).
[g]Predicted aqueous solubility, S in mol/dm^{-3} (acceptable range: −6.5–0.5).
[h]Predicted octanol/water partition coefficient (acceptable range: −2–6.5).
[i]Predicted human oral absorption on 0 to 100% scale (<25% is poor and >80% is high).

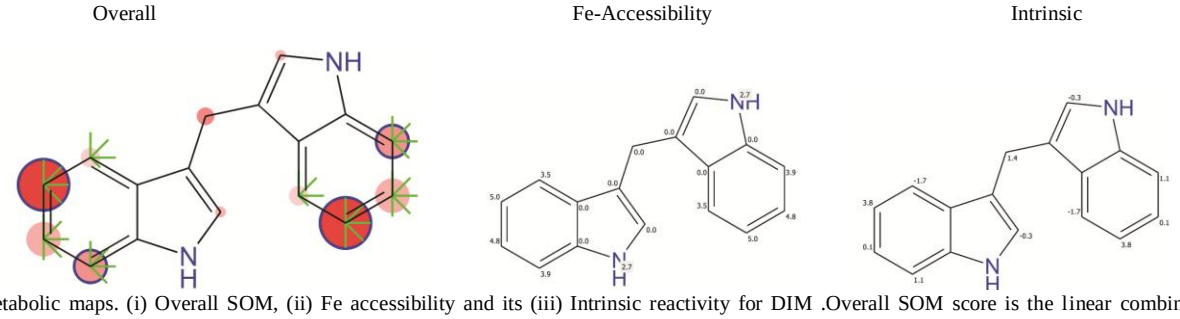

Fig. 3: Metabolic maps. (i) Overall SOM, (ii) Fe accessibility and its (iii) Intrinsic reactivity for DIM .Overall SOM score is the linear combination ofthe accessibility and the intrinsic reactivity larger scores mean higher reactivity. Fe accessibility (←): values indicate accessibility of the atoms to the iron center of CYP, full ray represents a unit of accessibility, with the length of the final ray representing the decimal portion. Intrinsic reactivity ( ): Labels the intrinsic reactivity of atoms, positive values are more reactive. The size of the circle indicates the overall SOM score, color of the circle indicates the atomic intrinsic reactivity and a blue ring around the circle indicates that the atom passed through the CYP filtering stage.

ADME and Toxicity analysis

Ligand based ADME/Toxicity prediction

The drug-like activity of the ligand molecule was categorized using ADME properties by QikProp module of Schrodinger. The ADME property of the indole-3-carbinol and DIM were evaluated with QikProp module of Schrodinger, shown in Table 2. The selected properties are known to influence metabolism, cell permeation, and bioavailability. All the predicted properties of the isolated compound was in the range for 95% of known oral drugs and also satisfy the Lipinski's rule of five to be considered as drug like potential.

Structure-based P450 site of metabolism

Cytochrome P450 enzymes are heme-containing enzymes, play an integral role in the metabolism pathway of drugs by undergoing a variety of reactions, such as hydroxylation, dealkylation, and double-bond oxidation that result in the degradation of small molecules (Liu *et al.,* 2013). A metabolic reaction can ensue at a highly reactive site of a molecule, on condition that it is properly oriented within the CYP enzyme to interact with the reaction center. Therefore, accessibility and intrinsic reactivity are the crucial aspects for a metabolic reaction to take place. For this reason metabolism of indole-3-carbinol and DIM were studied by induced fit docking with CYP2D6 and the results were analyzed on the basis of "Fe accessibility", "intrinsic reactivity" and "overall SoM (Site of Metabolism)". Details of these parameters, the metabolic maps of are illustrated in Figure 3. In Fe accessibility, labeled atoms are considered as the accessibility of the atoms to the iron. This is defined as the natural logarithm of the number of poses for the atom in which the atom was within 5 Å of Fe. Larger values of DIM indicate greater accessibility. The reactivity is predicted with a linear free energy approach based on the Hammett and Taft scheme, where the reactivity of a given atom is the sum of a baseline reactivity rate and a series of perturbations determined by the connectivity (Rydberg and Olsen, 2012). The intrinsic reactivity of DIM is quite high, according to the result, where positive values are more reactive, negative values are less reactive.

DISCUSSION

In few last decades, the implication of EGRF pathway in cancer progression has been suggested by various studies (Blume-Jensen and Hunter, 2001; Chan *et al.*, 2005). This consequence is often serious to the development of platinum drug resistance, in case of ovarian cancer treatment. Briefly, over expression of EGFR is linked with constitutive activation of STAT3 (signal transducers and activators of transcription 3) that confers resistance to chemotherapy-induced apoptosis in epithelial malignancies (Coley *et al.,* 2006; Duan *et al.,* 2006). The STAT3 protein, a member of the STAT family from latent cytoplasmic transcription factors, is phosphorylated by EGFR and other tyrosine kinases, which abnormally activated with a high frequency in many other human tumors, especially in ovarian cancer (Huang *et al.,* 2000; Burke *et al.,* 2001). The main fact is that the activation of STAT3 at Tyr-705 leads to accumulation of anti-apoptotic events, such as Bcl-2, Bcl-xL, and PI 3-kinase/Akt activity in the recurrent and resistant ovarian cancer (Richardson and Kaye, 2005) and granted constitutively active Stat3-mediated deregulation of gene expression is a well recognized mechanism to

promote malignant tumorigenesis, and tumor progression (Bowman *et al.*, 2000; Turkson, 2004), also it may be suggested that combination therapy like platinum drug with EGFR blocker may enhance the platinum chemo sensitivity in human ovarian cancer. Regarding this, we selected indole-3-carbinol and its active metabolite 3, 3′-diindolylmethane (DIM) to investigate the interactions and binding modes in active site of EGFR kinase domains. As described previously in result section, it may be concluded that the DIM has greater affinity towards the EGFR binding than the indole-3-carbinol, and will formed a stable protein ligand complex and may resulted inhibition. Moreover, numerous research had already established the mechanism of DIM, for inducing apoptosis, by inhibiting EGFR signaling in ovarian cancer (Kandala *et al.,* 2012), breast cancer and lung cancer cell (Rahimi *et al.,* 2010). Additionally, DIM has been exposed to decrease carcinogen-induced breast and lung tumor formation in rodent models of carcinogenesis with little toxicity (Chen *et al.*, 1998). Considering that, in our study, we tried to explore out the ADME and toxicity profiles both of two compounds, i.e., DIM and Indole-3-carbinol. As described in table 2, the ADME profile of DIM was quite low, though the concerning value of hERG K+ channel (which indicates the potential of a compound for cardiac toxicity) is high. This compound also processes high oral adsorption value. The metabolic map of DIM indicates the probability of deamination, as the amino group shows moderate Fe accessibility (Shown in Figure 3). This profile also suggested that DIM has the probability of aromatic hydroxylation due to their proximity to Fe also their intrinsic reactivity is high.

CONCLUSION

The current study is an attempt to explore out the therapeutic potentiality of 3,3'-diindolylmethane compound regarding the perspectives in platinum resistant ovarian cancer. In parallel, our experimental data supports the existing evidence in literature. Although, we explored out the pharmacokinetics profile of 3, 3'-diindolylmethane, further in vivo experiment is necessary to validate its biotransformation profile. However, the current work tries to address most of the variables in the dynamic drug design process right at the outset with the convenience of *In silico* tools in order to boost the potentiality of the selected molecule to serve as good leads in terms of optimum pharmacodynamic and toxicological attributes.

COMPETING INTERESTS

All authors declare that they have no competing interests.

REFERENCES

Adasme-Carreno F, Munoz-Gutierrez C, Caballero J, Alzate-Morales JH. Performance of the MM/GBSA scoring using a binding site hydrogen bond network-based frame selection: the protein kinase case. Phys Chem Chem Phys. 2014;16(27):14047-58.

Agarwal R, Kaye SB. Ovarian cancer: strategies for overcoming resistance to chemotherapy. Nat Rev Cancer. 2003;3(7):502-16.

Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, et al. The Protein Data Bank. Nucleic Acids Res. 2000;28(1):235-42.

Bible KC, Peethambaram PP, Oberg AL, Maples W, Groteluschen DL, Boente M, et al. A phase 2 trial of flavopiridol (Alvocidib) and cisplatin in platin-resistant ovarian and primary peritoneal carcinoma: MC0261. Gynecol Oncol. 2012;127(1):55-62.

Blume-Jensen P, Hunter T. Oncogenic kinase signalling. Nature. 2001;411(6835):355-65.

Bowman T, Garcia R, Turkson J, Jove R. STATs in oncogenesis. Oncogene. 2000;19(21):2474-88.

Bull Phelps SL, Schorge JO, Peyton MJ, Shigematsu H, Xiang LL, Miller DS, et al. Implications of EGFR inhibition in ovarian cancer cell proliferation. Gynecol Oncol. 2008;109(3):411-7.

Burke WM, Jin X, Lin HJ, Huang M, Liu R, Reynolds RK, et al. Inhibition of constitutively active Stat3 suppresses growth of human ovarian and breast cancer cells. Oncogene. 2001;20(55):7925-34.

Cataldo VD, Gibbons DL, Perez-Soler R, Quintas-Cardama A. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. N Engl J Med. 2011;364(10):947-55.

Chan JK, Pham H, You XJ, Cloven NG, Burger RA, Rose GS, et al. Suppression of ovarian cancer cell tumorigenicity and evasion of Cisplatin resistance using a truncated epidermal growth factor receptor in a rat model. Cancer Res. 2005;65(8):3243-8.

Chen I, McDougal A, Wang F, Safe S. Aryl hydrocarbon receptor-mediated antiestrogenic and antitumorigenic activity of diindolylmethane. Carcinogenesis. 1998;19(9):1631-9.

Ciska E, Verkerk R, Honke J. Effect of boiling on the content of ascorbigen, indole-3-carbinol, indole-3-acetonitrile, and 3,3'-diindolylmethane in fermented cabbage. J Agric Food Chem. 2009;57(6):2334-8.

Coley HM, Shotton CF, Ajose-Adeogun A, Modjtahedi H, Thomas H. Receptor tyrosine kinase (RTK) inhibition is effective in chemosensitising EGFR-expressing drug resistant human ovarian cancer cell lines when used in combination with cytotoxic agents. Biochem Pharmacol. 2006;72(8):941-8.

Dash R, Ahsan T, Hosen SZ, Rahman MG, Emran TB, Muhammad M, et al. Evolution of selective COX-2 inhibitor from Alangium salvifolium: an *In silico* approach. Journal of Applied Pharmaceutical Science Vol. 2015;5(04):089-93.

Dash R, Emran TB, Uddin MM, Islam A, Junaid M. Molecular docking of fisetin with AD associated AChE, ABAD and BACE1 proteins. Bioinformation. 2014;10(9):562-8.

Dash R, Hosen SMZ, Sultana T, Junaid M, Majumder M, Ishat I, et al. Computational Analysis and Binding Site Identification of Type III Secretion System ATPase from Pseudomonas aeruginosa. Interdiscip Sci Comput Life Sci. 2015 2015/08/15:1-9.

Duan Z, Foster R, Bell DA, Mahoney J, Wolak K, Vaidya A, et al. Signal transducers and activators of transcription 3 pathway activation in drug-resistant ovarian cancer. Clin Cancer Res. 2006;12(17):5055-63.

Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, et al. Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. J Med Chem. 2004;47(7):1739-49.

Friesner RA, Murphy RB, Repasky MP, Frye LL, Greenwood JR, Halgren TA, et al. Extra precision glide: docking and scoring incorporating a model of hydrophobic enclosure for protein-ligand complexes. J Med Chem. 2006;49(21):6177-96.

Hennessy BT, Coleman RL, Markman M. Ovarian cancer. Lancet. 2009;374(9698):1371-82.

Herzog TJ. Recurrent ovarian cancer: how important is it to treat to disease progression? Clin Cancer Res. 2004;10(22):7439-49.

Huang M, Page C, Reynolds RK, Lin J. Constitutive activation of stat 3 oncogene product in human ovarian carcinoma cells. Gynecol Oncol. 2000;79(1):67-73.

Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90.

Kandala PK, Srivastava SK. Activation of checkpoint kinase 2 by 3,3'-diindolylmethane is required for causing G2/M cell cycle arrest in human ovarian cancer cells. Mol Pharmacol. 2010;78(2):297-309.

Kandala PK, Wright SE, Srivastava SK. Blocking epidermal growth factor receptor activation by 3,3'-diindolylmethane suppresses ovarian tumor growth in vitro and in vivo. J Pharmacol Exp Ther. 2012;341(1):24-32.

Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell. 2010;141(7):1117-34.

Liu X, Shen Q, Li J, Li S, Luo C, Zhu W, et al. *In silico* prediction of cytochrome P450-mediated site of metabolism (SOM). Protein Pept Lett. 2013;20(3):279-89.

Natarajan A, Sugumar S, Bitragunta S, Balasubramanyan N. Molecular docking studies of (4Z, 12Z)-cyclopentadeca-4, 12-dienone from Grewia hirsuta with some targets related to type 2 diabetes. BMC complementary and alternative medicine. 2015;15(1):73.

Rabik CA, Dolan ME. Molecular mechanisms of resistance and toxicity associated with platinating agents. Cancer Treat Rev. 2007;33(1):9-23.

Rahimi M, Huang KL, Tang CK. 3,3'-Diindolylmethane (DIM) inhibits the growth and invasion of drug-resistant human cancer cells expressing EGFR mutants. Cancer Lett. 2010;295(1):59-68.

Rahman KW, Sarkar FH. Inhibition of nuclear translocation of nuclear factor-{kappa}B contributes to 3,3'-diindolylmethane -induced apoptosis in breast cancer cells. Cancer Res. 2005;65 (1):364-71.

Richardson A, Kaye SB. Drug resistance in ovarian cancer: the emerging importance of gene transcription and spatio-temporal regulation of resistance. Drug Resist Updat. 2005;8(5):311-21.

Rydberg P, Olsen L. Predicting drug metabolism by cytochrome P450 2C9: comparison with the 2D6 and 3A4 isoforms. ChemMedChem. 2012;7(7):1202-9.

Scaltriti M, Baselga J. The epidermal growth factor receptor pathway: a model for targeted therapy. Clin Cancer Res. 2006;12(18):5268-72.

Slatnik CL, Duff E. Ovarian cancer: Ensuring early diagnosis. Nurse Pract. 2015;40(9):47-54.

Turkson J. STAT proteins as novel targets for cancer drug discovery. Expert Opin Ther Targets. 2004;8(5):409-22.

Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol. 2001;2(2):127-37.

How to cite this article:

Dash R, Hosen SMZ, Karim MR, Kabir MSH, Hossain MM, Junaid M, Islam A, Paul A, Khan MA. *In silico* analysis of indole-3-carbinol and its metabolite DIM as EGFR tyrosine kinase inhibitors in platinum resistant ovarian cancer vis a vis ADME/T property analysis. J App Pharm Sci, 2015; 5 (11): 073-078.