Archives of Pharmaceutical Sciences and Research
Vol 16 Issue 3 10–20 September 2026
E-ISSN 0975-2633 | PRINT ISSN 0975-5284
Research Article

IN SILICO ADME ANALYSIS AND MOLECULAR DOCKING OF PHYTOCHEMICALS FROM MORINDA CITRIFOLIA WITH ONCOGENIC SHP2 PROTEIN

Chandru P[1]*, Nandhana R[1], Ganapathy CA[2], Selvamuthukumar R[3], Saminathan C[4]

*[1] B. Pharm, Mayor Radhakrishnan College of Pharmacy, The Tamilnadu Dr MGR Medical University, Cuddalore – 607001.

[2] Professor, Mayor Radhakrishnan College of Pharmacy, Affiliated to The Tamilnadu Dr MGR Medical University, Cuddalore – 607001

[3] Associate Professor, Mayor Radhakrishnan College of Pharmacy, Affiliated to The Tamilnadu Dr MGR Medical University, Cuddalore – 607001

[4] Professor, Mayor Radhakrishnan College of Pharmacy, Affiliated to The Tamilnadu Dr MGR Medical University, Cuddalore – 607001

ABSTRACT

SHP2 (Src homology 2 domain-containing phosphatase 2) is a protein tyrosine phosphatase that plays a major role in the activation of various cell signaling pathways such as RAS/Raf/MAPK, PI3K/AKT, mTOR. Over activating mutation or excessive overexpression of SHP2 is linked with metastasis and tumorigenesis. Identification of active site inhibitors for SHP2 protein is quite challenging as the catalytic site is enriched with a positively charged environment. To overcome this, allosteric inhibition of the SHP2 protein in auto-inhibited conformation is considered. Here, we used the phytochemicals which are found to be present in the leaf extract of *Morinda citrifolia* to target the SHP2 protein. The ADME properties of those phytochemicals were studied using the SwissADME tool. Molecular docking of potent phytochemicals was performed with SHP2 protein (PDB - 5EHR) using AutoDock tools. 18 phytochemicals which are found to be present in the leaf extract of *Morinda citrifolia* were selected for SwissADME analysis and result showed that four phytochemicals (Minaprine, Mycophenolic acid, Pilocarpine and Scopolamine) were found to possess drug-likeness and good oral bioavailability. Molecular docking of Minaprine, Mycophenolic acid, Pilocarpine and Scopolamine with SHP2 protein shows a good binding affinity of -9.6, -9.32, -6.81and -9.05 kcal/mol at the allosteric site, respectively. This shows that these phytochemicals can be used for the development of potent allosteric inhibitors of SHP2 in the treatment of cancer. In summary, the ADME properties and docking studies with SHP2 protein shown that Minaprine, Mycophenolic acid, Pilocarpine and Scopolamine which is found in the leaf extract of *Morinda citrifolia* shows good oral bioavailability and inhibitory action. Therefore, these phytochemicals can be used for the treatment of cancer targeting SHP2 protein.

Keywords: *Morinda citrifolia*, SHP2, Molecular docking, ADME

INTRODUCTION

The regulation of the signaling cascade (from initiation to termination) in the cellular process is based on the status of phosphorylation of the tyrosine residue, which is found in most of the signaling proteins. This phosphorylation is greatly influenced by two proteins namely tyrosine kinase and tyrosine phosphatase which is responsible for the phosphorylation and dephosphorylation. Targeting the proteins that are involved in the phosphorylation/dephosphorylation of tyrosine within the signaling pathway will act as a promising agent in drug development for different cancers as these proteins can activate multiple growth factors for uncontrolled cell proliferation.

Currently, inhibitors for protein tyrosine kinase have been used to treat cancers. However, inhibitors targeting protein tyrosine phosphatase are unexplored due to a lack of understanding about the biological function, selectivity, and poor pharmacokinetics of the available inhibitors. Src homology-2 domain-containing protein tyrosine phosphatase (SHP) is a family of protein tyrosine phosphatase which consists of two proteins - SHP1 and SHP2.

SHP2 is found in the cytoplasm and is activated by different kinds of receptor

tyrosine kinases to promote cell signaling and is a key component of various oncogenic signaling cascades such as RAS/Raf/MAPK, PI3K/AKT and mTOR pathways. SHP2 is an important factor in inducing many cellular functions such as cell proliferation, migration, differentiation and regulation of the cell cycle because of its catalytic activity. SHP2 has two domains (N-SH2 and C-SH2), a C-terminal which have two sites for tyrosine phosphorylation (Tyr542 and Tyr580) and a catalytic domain (PTP). In the inactive state, the PTP domain is autoinhibited by the N-SH2 and two sites for tyrosine phosphorylation are away from the N-SH2, C-SH2, and PTP interface. The binding of phosphotyrosine (pTyr) to N-SH2, disrupts the interaction between the N-SH2 and PTP domain, thereby SHP2 protein is activated.

The current research work aimed to evaluate the potential of phytochemicals from *Morinda citrifolia* as inhibitors of the SHP2 protein using computational approaches. With objectives of to select phytochemicals reported from *Morinda citrifolia* for analysis. To assess their pharmacokinetic properties using SwissADME . To prepare ligand molecules and the target protein structure (PDB ID: 5EHR) . To perform molecular docking using AutoDock. To analyse binding affinity and interaction patterns with SHP2 . To identify promising compounds with potential anticancer activity.

MATERIALS AND METHODS

Materials

The three-dimensional structure of the SHP2 protein (PDB ID: 5EHR) was obtained from the Protein Data Bank. Phytochemical compounds related to *Morinda citrifolia* were identified through literature survey. A total of eighteen compounds were selected for further study. The chemical structures of the selected compounds were retrieved from the PubChem database. Swiss ADME was used to analyze pharmacokinetic properties of the compounds. AutoDock software was employed to perform molecular docking studies.

Methods

Phytochemicals in *Morinda citrifolia*

The phytochemicals which was found to be present in the leaf extract *M. citrifolia* were obtained from studies carried out by Arunachalam, et al., (2015) , Lim, et al., (2017) and Vuanghao & Laghari (2017) with which ADME analysis and allosteric inhibition of SHP2 protein via *in silico* method are studied.

ADME Analysis

The pharmacokinetic properties, drug-likeness, physiochemical, water solubility and lipophilicity of the identified phytochemicals from *M. citrifolia* extract were estimated with the help of the SwissADME online server (http://www.swissadme.ch/) which is used for the prediction of ADME (absorption, distribution, metabolism, and excretion) properties.

In Silico Analysis

Ligand Preparation

The 2D structure of the four phytochemicals-Minaprine, Pilocarpine, Mycophenolic acid and Scopolamine were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/). Energy minimization was performed using Avogadro software , to remove the energy clashes between the atoms of the ligands. The energy minimized ligands were saved in .pdb format for further docking with SHP-2 protein.

Preparation of SHP-2 protein

The crystallographic 3D structure of the SHP-2 protein complex with the allosteric inhibitor SHP099 with a resolution of 1.70 Å was downloaded from the RCSB Protein Data Bank (PDB ID: 5EHR). The protein was prepared by removing the crystallized inhibitor (SHP009) and exterminating residual molecules and water using Pymol.

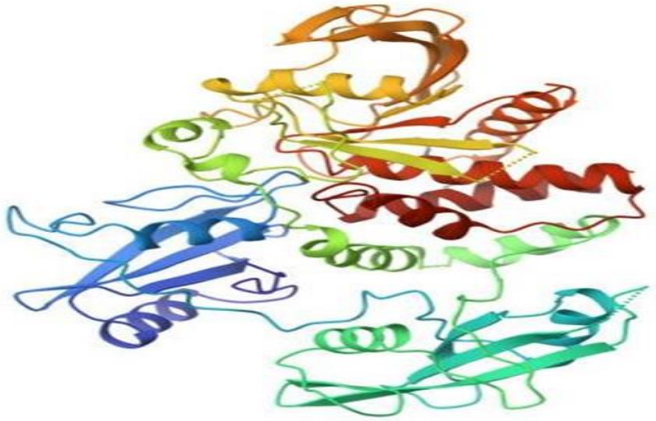


Figure No. 1 Crystal Structure of SHP2 in auto inhibited conformation (PDB2SHP)

Molecular docking

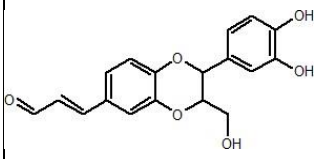
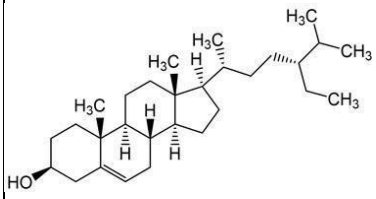
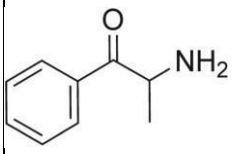
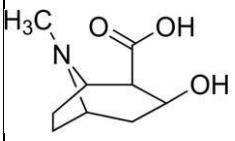
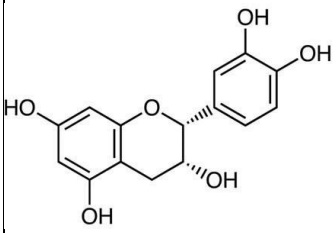
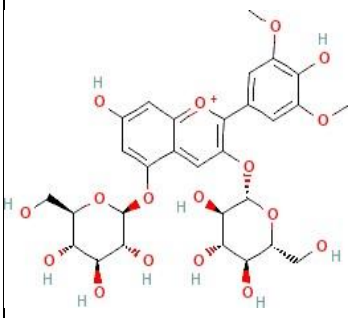
AUTODOCK tool is the most widely used program for performing docking studies. AUTODOCK 4.2 is used to study the interaction between the phytochemicals and the SHP-2 protein. Explicit hydrogen atoms were added and Kollmann and Gasteiger charges were assigned to the protein. The prepared protein is saved in a pdb format. The allosteric site of the SHP-2 protein is obtained from the previous literature work . Autogrid is used to generate the grid box around the allosteric site of the protein and it was specified with the x, y and z coordinates of 22.585 x 41.238 x 5.392. The docking parameters are set at LGA runs of 100, the population size of 150 and the docking was carried out with the energy minimized ligands. As per the docking protocol, the conformations of protein-ligand complex were ranked based on the binding affinity and the conformation with the least binding energy was taken as the best docking score. The interaction between four phytochemicals and SHP2 protein was visualized using PyMOL.

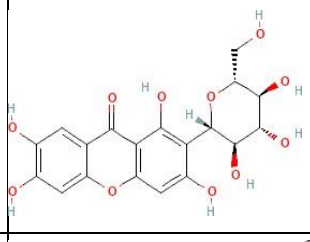
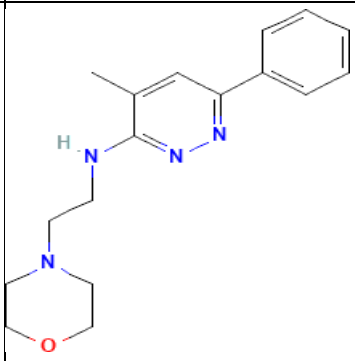
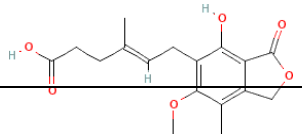
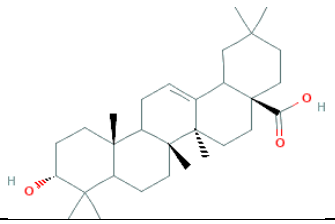
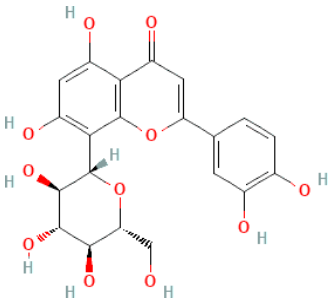
RESULTS

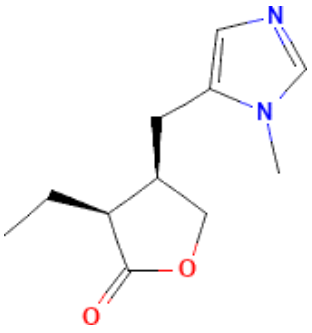
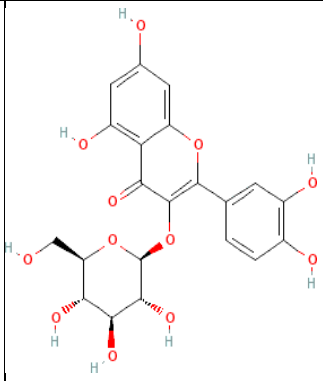
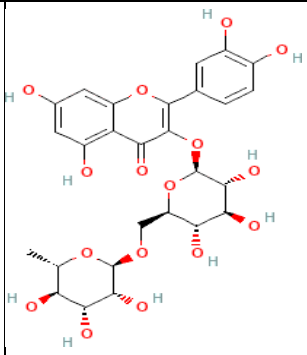
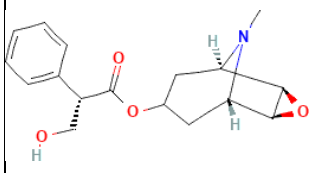
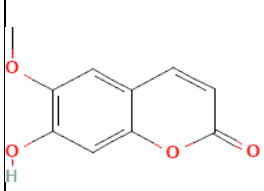
ADME Properties of Identified Phytochemical from *M. citrifolia* extract

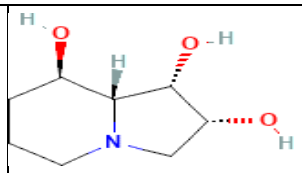
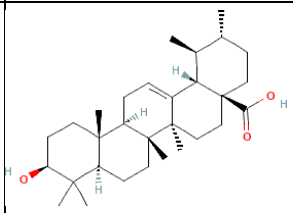
The list of phytochemicals which has been found to be present in the leaves of *M. citrifolia* is shown in **(Table)**. ADME parameters of chemical compounds play an important role in the process of drug discovery and development. The ADME properties (absorption, distribution, metabolism, and excretion) of the 18 phytochemicals present in the leaf extract of *M. citrifolia* were studied using SwissADME and the results were given in supplementary **(Table No. 2).** The drug-likeness properties of the phytochemicals in *M. citrifolia* leaf extract was displayed in the bioavailability radar **(Figure No. 2).** The phytochemicals which fall under the pink region of the polygon structure exhibit good oral bioavailability and obeys six key physiochemical properties. From the bioavailability radar, Minaprine, Mycophenolic acid, Pilocarpine and Scopolamine were found to possess good oral bioavailability.

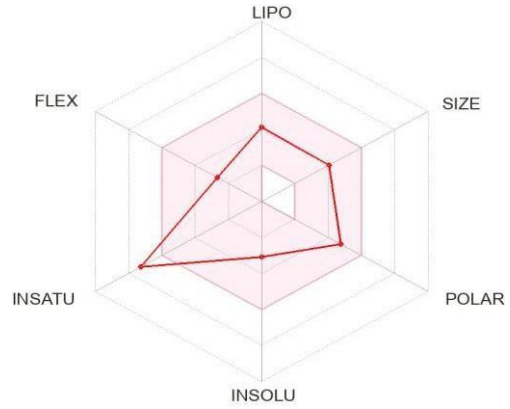
Table 1 List of Phytochemicals identified in the leaf extract of *Morinda citrifolia*

S. No.	Compound	Canonical SMILES	PubChem ID	Chemical structure	References
1	**Americanin A**	C1=CC2=C(C=C1C=CC=O)OC(C(O2)C3=CC(=C(C=C3)O)O)CO	5459018		[1]
2	**Beta Sitosterol**	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C	222284		[3]
3	**Cathinone**	CC(C(=O)C1=CC=CC=C1)N	62258		[3]
4	**Ecgonine**	CN1C2CCC1C(C(C2)O)C(=O)O	91460		[3]
5	**Epicatechin**	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O	72276		[2]
6	**Malvidin-3,5-Di glucoside**	COC1=CC(=CC(=C1O)OC)C2=C(C=C3C(=CC(=C3=[O+]2)O)OC4C(C(C(C(O4)CO)O)O)O)O)OC5C(C(C(C(O5)CO)O)O)O	441765		[3]

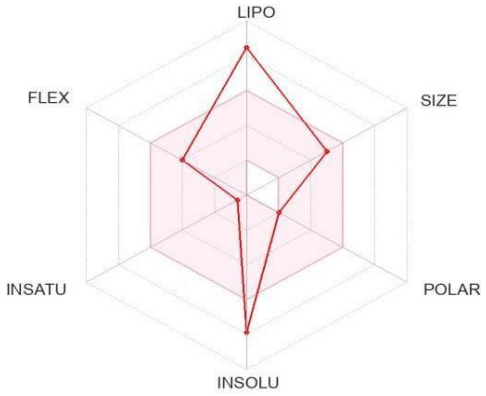
7	**Mangiferin**	C1=C2C(=CC(=C1O)O)OC3=C(C2=O)C(=C(C(=C3)O)C4C(C(C(C(O4)CO)O)O)O)O	5281647		[3]
8	**Minaprine**	CC1=CC(=NN=C1NCCN2CCOCC2)C3=CC=CC=C3	4199		[3]
9	**Mycophenolic Acid**	CC1=C2COC(=O)C2=C(C(=C1OC)CC=C(C)CCC(=O)O)O	446541		[3]
10	**OleanoicAcid**	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)C)C)C2C1)C)C(=O)O)C	485707		[3]
11	**Orientin**	C1=CC(=C(C=C1C2=CC(=O)C3=C(O2)C(=C(C=C3O)O)C4C(C(C(C(O4)CO)O)O)O)O)O	5281675		[3]

12	**Pilocarpine**	CCC1C(COC1=O)CC2=CN=CN2C	5910		[3]
13	**Quercetin3-O- Beta-D-Glucopyranoside**	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)OC4C(C(C(C(O4)CO)O)O)O)O)O	5280804		[1]
14	**Rutin**	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O	5280805		[3]
15	**Scopolamine**	CN1C2CC(CC1C3C2O3)OC(=O)C(CO)C4=CC=CC=C4	3000322		[3]
16	**Scopoletin**	COC1=C(C=C2C(=C1)C=CC(=O)O2)O	5280460		[2]
17	**Swainsonine**	C1CC(C2C(C(CN2C1)O)O)O	51683		[3]

					
18	**UrsolicAcid**	CC1CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)C)C)C2C1C)C)C(=O)O	64945		[1]

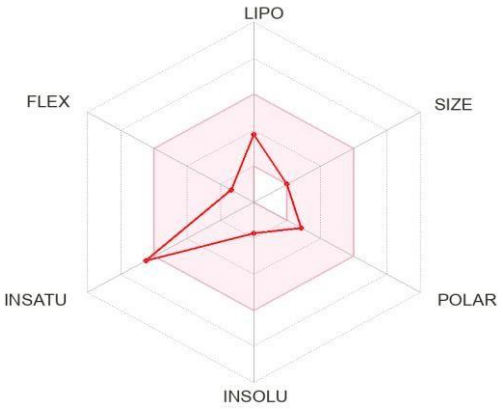


1. Americanin A

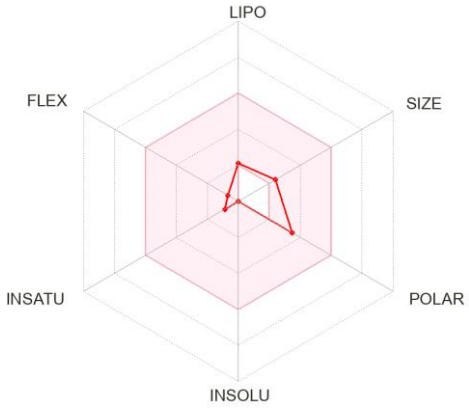


2. Beta sitosterol

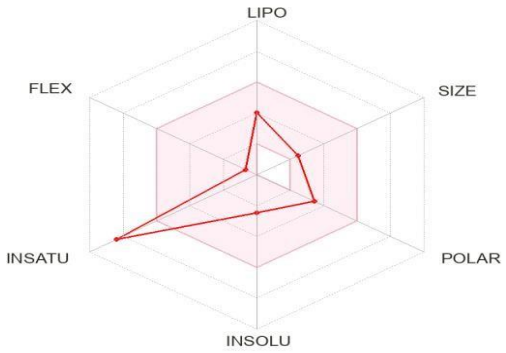
Figure No. 2 Bioavailability radar of phytochemicals presents in the leaf extract of *Morinda citrifolia*



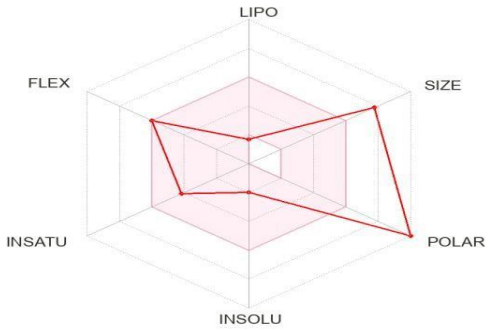
3. Cathinone



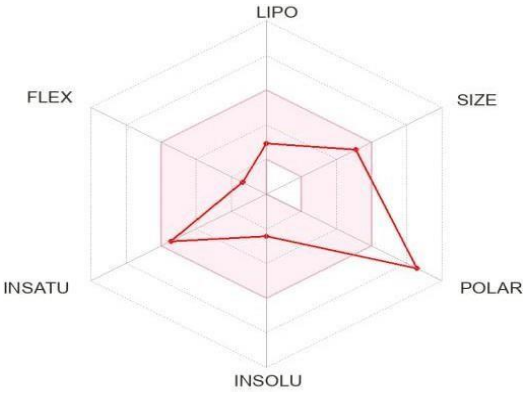
4. Ecgonine



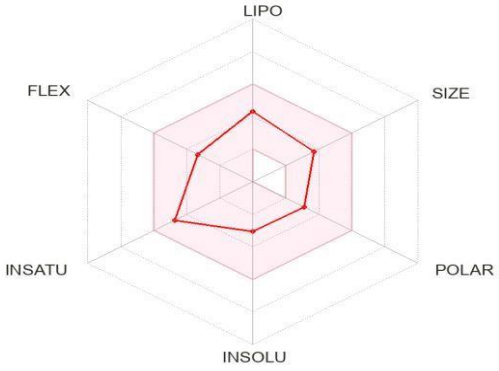
5.Epicatechin



6. Malvidin-3,5-diglucoside



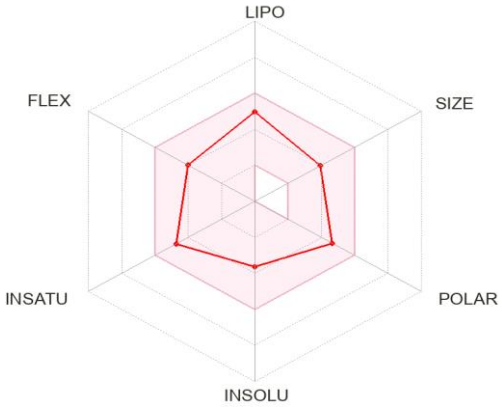
7. Mangiferin



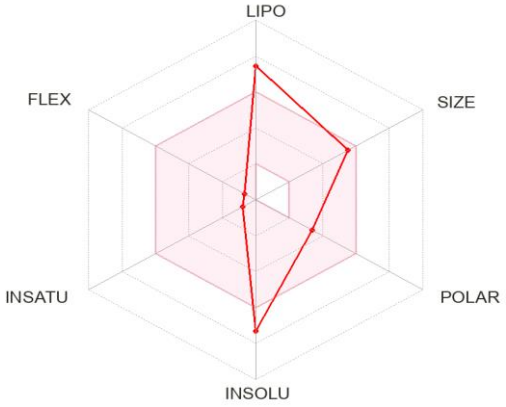
8. Minaprine

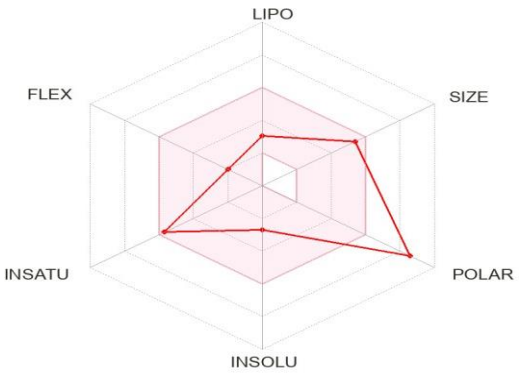
Figure No. 2 Bioavailability radar of phytochemicals presents in the leaf extract of *Morinda citrifolia*

9. Mycophenolic Acid

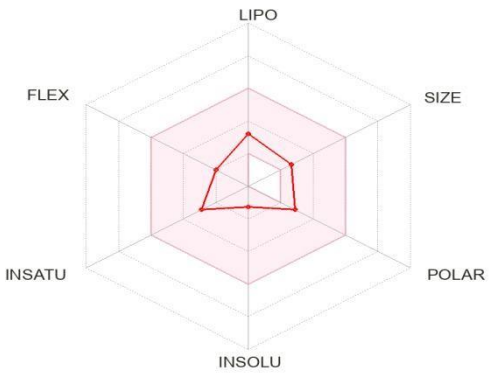


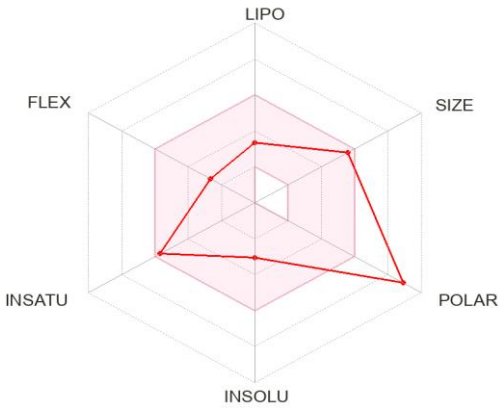
10. Oleanoic Acid



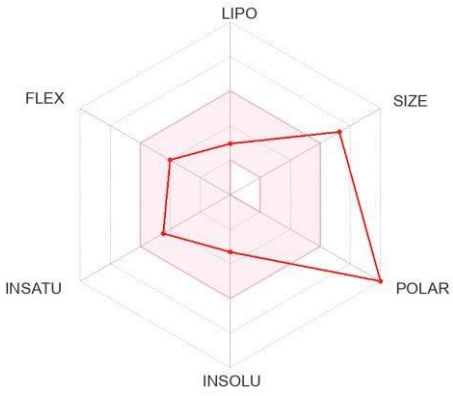


11- Orientin



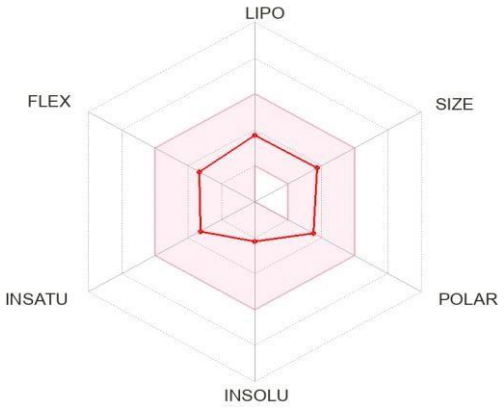


12-Pilocarpine

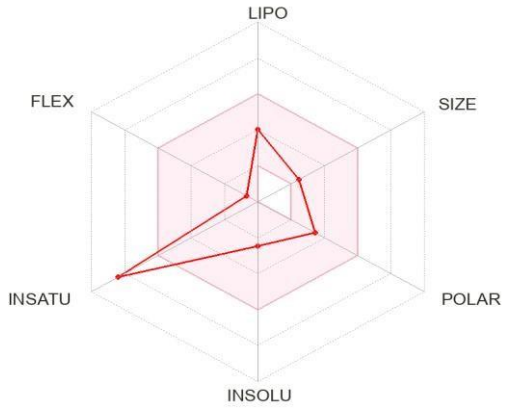


13-Quercentin 3-0-Beta-D-13- Glucopyranoside

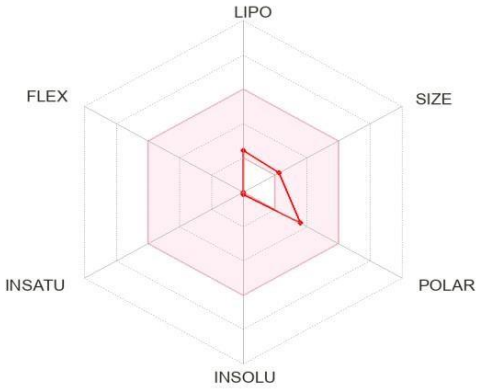
14- Rutin



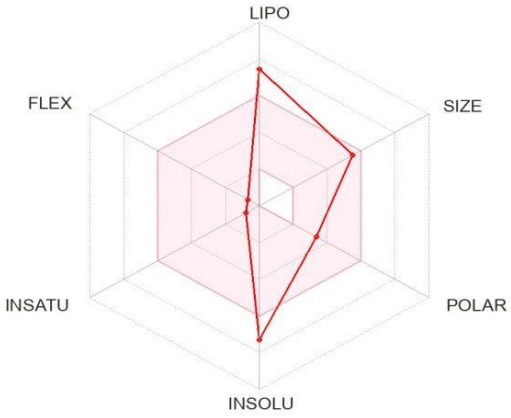
15- Scopolamine



16- Scopoletin



17- Swainsonine



18-Ursolic Acid

Figure No. 2 Bioavailability radar of phytochemicals presents in the leaf extract of *Morinda citrifolia*

The phytochemicals which fall under the pink region of the polygon structure exhibit good oral bioavailability and obeys six key physiochemical properties. From the bioavailability radar, Minaprine, Mycophenolic acid, Pilocarpine and Scopolamine were found to possess good oral bioavailability.

SUMMARY AND CONCLUSION

SUMMARY

The identification and development of potent SHP2 inhibitors with good oral bioavailability and selectivity poses a great challenge due to the increased biological function of SHP2 in cancer and immune signaling. In our study, ***Morinda citrifolia***which has already been found to possess anticancer activity is considered in order to predict the novel phytochemicals in the leaves that exert good oral bioavailability as well as inhibition of SHP2 protein. Minaprine, Mycophenolic acid, Pilocarpine and Scopolamine have good oral bioavailability and bind into the central tunnel of SHP2 protein and maintain it in the auto-inhibited conformation. Thus, these phytochemicals act as an allosteric inhibitor of SHP2 and act as a lead molecule in the synthesis of SHP2 allosteric inhibitors.

CONCLUSION

This study focuses on identifying potential anticancer compound *from* ***Morinda***

citrifolia(commonly known as noni) using computational methods such as ADME analysis and molecular docking against the SHP2 protein .

REFERENCES

1. T. Hunter, Tyrosine phosphorylation: thirty years and counting, Curr. Opin. Cell Biol.
2. 21 (2009) 140–146.
3. N.K. Tonks, Protein tyrosine phosphatases: from genes, to function, to disease, Nat. Rev. Mol. Cell Biol. 7 (2006) 833–846.
4. J.-J. Ventura, Á.R. Nebreda, Protein kinases and phosphatases as therapeutic targets in cancer, Clin. Transl. Oncol. 8 (2006) 153–160.
5. J. Zhang, F. Zhang, R. Niu, Functions of Shp2 in cancer, J. Cell. Mol. Med. 19 (2015)
6. 2075–2083.
7. D. Barford, B.G. Neel, Revealing mechanisms for SH2 domain mediated regulation of the protein tyrosine phosphatase SHP-2, Structure. 6 (1998) 249–254.
8. P. Hof, S. Pluskey, S. Dhe-Paganon, M.J. Eck, S.E. Shoelson, Crystal structure of the tyrosine phosphatase SHP-2, Cell. 92 (1998) 441–450.
9. Prahallad, G.J.J.E. Heynen, G. Germano, S.M. Willems, B. Evers, L. Vecchione, V. Gambino, C. Lieftink, R.L. Beijersbergen, F. Di Nicolantonio, PTPN11 is a central node in intrinsic and acquired resistance to targeted cancer drugs, Cell Rep. 12 (2015) 1978– 1985.
10. V.E. Schneeberger, Y. Ren, N. Luetteke, Q. Huang, L. Chen, H.R. Lawrence, N.J.
11. Lawrence, E.B. Haura, J.M. Koomen, D. Coppola, Inhibition of Shp2 suppresses mutant
12. EGFR-induced lung tumors in transgenic mouse model of lung adenocarcinoma, Oncotarget. 6 (2015) 6191.
13. X. Yuan, H. Bu, J. Zhou, C.-Y. Yang, H. Zhang, Recent advances of SHP2 inhibitors in cancer therapy: current development and clinical application, J. Med. Chem. 63 (2020) 11368–11396.
14. D. Shen, W. Chen, J. Zhu, G. Wu, R. Shen, M. Xi, H. Sun, Therapeutic potential of targeting SHP2 in human developmental disorders and cancers, Eur. J. Med. Chem. 190 (2020) 112117.