EXCELLENT PUBLISHERS

International Journal of Current Research and Academic Review

ISSN: 2347-3215 Special Issue-4 (October-2017)

Journal home page: http://www.ijcrar.com

Prediction of Binding Affinity and Molecular Interaction of Mcp-1 with Carbazole Alkaloids from *Murraya koenigii*

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KEYWORDS

Wound healing, Carbazole alkaloids, *Murraya koenigii*, MCP-1, Molecular Docking

A B S T R A C T

Murraya koenigii is an ethno medicinal plant, native to India which exhibits diverse biological activities. In ancient systems of medicine including Ayurveda, Siddha and Unani, *M. koenigii* has vast number of therapeutic applications. Carbazole alkaloids are the major constituents of the plant which are known to exhibit cytotoxic, antioxidative, antimutagenic and anti-inflammatory activity. They are abundantly present in its stem, leaf and root extracts. Carbazole alkaloids from *M. koenigii* possess wound healing property. Wounds are the disruption of normal anatomic structure and function of tissues. It is an injury to the body that involves damage to underlying tissues. Wound healing is a normal biological process achieved through hemostasis, inflammation, proliferation and remodeling. It is a complex series of reactions and interactions among cells and "mediators". The Monocyte / Macrophage chemoattractant protein-1 (MCP-1) contribute to the development of mature vessels and collateral arteries. It plays a key role in extravascular wound healing following injury. They induce monocytes to leave the blood stream and mediate the recruitment of monocytes in inflammatory process. Many growth factors are involved in wound healing, a beneficial growth factor which is widely used in scarless wound healing is FGF-2. It is a member of a large family of protein which stimulates the growth and development of new blood vessel (angiogenesis) that contribute to normal wound healing and tissue development. The blood vessel formation is potentiated by the MCP-1 protein. The ideal way to reduce the wound is to enhance the activity of MCP-1. The 3D structure of MCP-1 is subjected to molecular docking with Carbazole alkaloids from *M. koenigii*. Docking scores indicates that Mahanimbilol in *M. koenigii* show three interactions with MCP-1 protein, hence it is considered as effective and natural therapeutic agent to heal the wounds.

Introduction

Murraya koenigii, commonly known as kariveppilai in Tamil, found to be native mainly to India and Srilanka. Additionally, it can be found in some other South Asian

countries. Of the 14-global species belonging to the genus *Murraya*, only two are available in India, namely *Murraya koenigii* and *Murraya poniculata* (Banu *et al.,* 2016) and it is a rich source of Carbazole alkaloids. The Carbazole alkaloids constitute an important class of naturally occuring heterocycles, isolated from the Rutaceae family. They were isolated as natural products from *Murraya koenigii* that exhibited strong pharmacological activity. The major constituent of the plant is known to possess cytotoxic, anti-oxidative, antimutagenic, anti-inflammatory activites. The anti-oxidant and anti-microbial activity of curry leaves is attributed to Mahanine, Murrayanol, Murrayamine M, Murrayamine J, and Mahanimbilol. This study is a novel approach emphasizing the significance of natural products like Carbazole alkaloids as a prime solution to unanswered question like the treatment of wounds.

Wound is a break or "disruption" in the continuity of a body tissue that is followed by restoration. Wound healing is a normal biological process in human body which is achieved through four precisely and highly programmed phases: Hemostasis, Inflammation, Proliferation and Remodeling (Guo *et al.,* 2010). The interaction between cells and the components of extra cellular matrix (ECM) are responsible for tissue repair and wound healing. Wound remains a challenging clinical problem and correct, efficient wound management is essential.

Much effort has been focused on wound care with an emphasis on new therapeutic approaches and the development of technologies for acute and chronic wound management. It involves multiple cell populations, the extracellular matrix and the action of soluble mediators such as growth factors and cytokines. Many growth factors involved in healing process. FGF-2 is the most important growth factor in wound healing. Fibroblast growth factor (FGF-2) is a member of a large family of proteins that bind heparin and modulate the function of a wide range of cell types. FGF-2 stimulates the growth and development of cells. FGF-2 play a role in granulation tissue formation, reepithelization and tissue remodeling (Wellstein *et al.,* 2000, Clark *et al.,* 1996). Within granulation tissue, angiogenesis is potentiated by FGF-2 and by the MCP-1 (Belperio *et al.,* 2000). MCP-1 has key role in extravascular wound healing that may have different implications as compared to its intravascular role in the pathogenesis (Dewald *et al.,* 2005) and can mediate the recruitment of monocytes in several inflammatory diseases. MCP-1 expression was strongly stimulated by FGF-2 gene transfer and MCP-1 / CCR_2(C-C Chemokine receptor type 2), which played a critical biological role in FGF-2 mediated recovery of blood flow. The MCP-1 /CCR_2 system known as proinflammatory / arteriogenic pathway plays a critical role in FGF-2 mediated therapeutic neovascularization. FGF-2 targets to enhance the inflammatory / arteriogenic pathway (MCP-1) resulting in efficient recovery of blood flow, via divergent signal transduction pathway (TakaakiFujii *et al.,* 2006).

Docking is a process by which one can predict the significant orientation of one molecule to a second when bound to each other to form a stable complex. It is mostly used for finding the binding between the ligand and the protein. The information obtained from the docking technique can be used to suggest the binding energy, free energy and stability of complex. At present, docking technique is utilized to predict the tentative binding parameter of ligand – receptor complex beforehand (Shafia Mir *et al.,* 2017).

Materials and Methods

Preparation of Protein Structure

The three-dimensional structure of target protein was retrieved from Protein Data Bank (PDB) of uniprot (universal protein). This Structure was downloaded from PDB format. Uniprot is a freely accessible database of protein sequence and functional information. Protein Data Bank (PDB) (http://www.rcsb.org/pdb) obtained by X-ray crystallography or NMR spectroscopy are freely accessible (Helen *et al.,* 2008).

Preparation of Ligand Structure

The *Murraya koenigii* compounds (main carbazole alkaloids) were downloaded from pubchem in the MDL mol format. Pubchem is a database of chemical molecules and their activities against biological assays. The system is maintained by the National Center for Biotechnology Information (NCBI). The ligands were designed using Chemsketch and their 2D structure was converted to 3D structures using Chem3D ultra 6.1 in ACD/Labs (Dhananjayan Karthik *et al.,* 2014) (https://pubchem.ncbi.nlm.nih.gov).

Molecular Docking Analysis

A computational ligand-target docking approach was used to analyze structural complexes of the MCP-1 (target) with Mahanine, Mahanimbilol, Murrayanol, Murrayamine-M, and Murrayamine-J (ligand) to understand the structural basis of this protein target specificity (Syed Aun Muhammad *et al.,* 2015). Docking was carried out by AutoDock1.5.6 based on scoring functions. Finally, it shows the interaction with number of hydrogen bond and binding energy. Auto Dock is a suite of automated docking tools. It uses Genetic Algorithms for the conformational docking studies (Helen *et al.,* 2008). The structures downloaded in PDBQT format were then converted to PDB format using OPEN BABEL 2.3.2 and were used for docking analysis (Sathish Kumar *et al.,* 2010).

Discovery Studio Visualizer

Molecular visualization is a key aspect of the analysis and communication of modelling studies (http://accelrys.com).

Results and Discussion

Sequence retrieval MCP-1

The sequence of Monocyte / Macrophage chemoattractant protein-1 (MCP-1) is retrieved from uniprot database and sequence accession number is P13500.

Structure retrieval

Three- dimensional structure of the MCP-1 is retrieved from PDB database and its PDB ID is 3IFD. The structure of MCP-1 is downloaded from PDB in pdb format and stored. That structure is visualized by using Rasmol.

Preparation of ligands

For docking analysis 5 Carbazole alkaloids from *M. koenigii* were selected. The 2D structures of the ligands were generated using ACD /Chemsketch tools. This software contains tools for 2D cleaning, 3Doptimization, and viewing. These data are saved as a molecular format file (MDL MOL format). The converter tool (Open Babel) is used to convert this file into the PDB format and is used during docking analysis. The structure and molecular formula of Carbazole Alkaloids of *Murraya koenigii* was shown in Table 1.

Table.1 Compounds extracted from *Murraya koenigii*

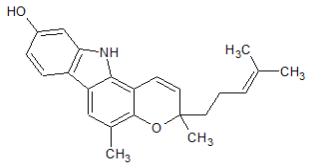
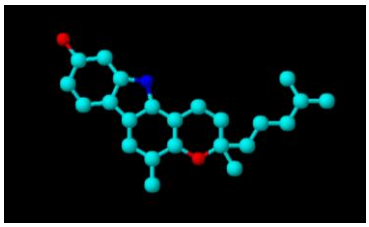
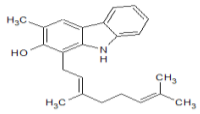
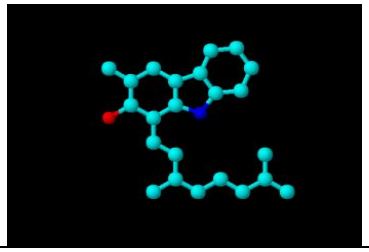
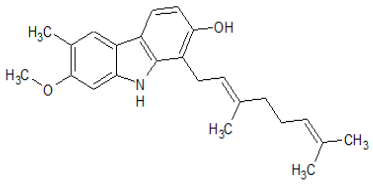
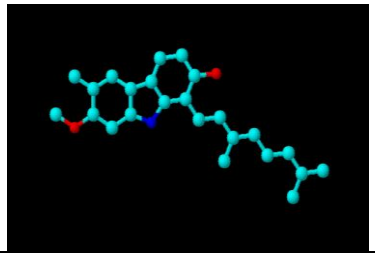
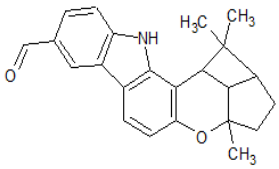
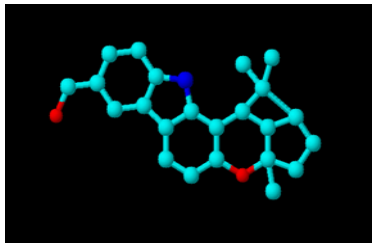
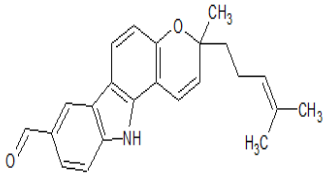
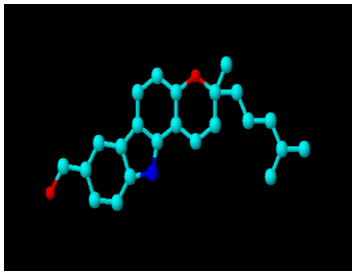
S.NO	COMPOUND NAME	MOLECULAR FORMULA	2D STRUCTURE	3D STRUCTURE
1	Mahanine	$C_{23}H_{25}NO_2$		
2	Mahanimbilol	$C_{23}H_{27}NO$		
3	Murrayanol	$C_{24}H_{29}NO_2$		
4	Murrayamine-M	$C_{23}H_{23}NO_2$		
5	Murrayamine-J	$C_{23}H_{23}NO_2$		

Table.2 Docking interaction between MCP-1 and Mahanimbilol

MCP-1		Mahanimbilol	Distance (A)	Docking energy (Kcal / mol)
Residue	**Atom**			
THR-10	OG1	N	3.3	-7.77
THR-32	N	O	2.9	
SER-33	N	O	3.0	
PRO-8	O	N	3.4	

Table.3 Docking interaction between MCP-1 and Murrayamine-M

MCP-1		Murrayamine-M	Distance (A)	Docking energy (Kcal / mol)
Residue	**Atom**			
ASN17	N	O	3.0	-7.99
THR-16	OG1	O	3.4	

Table.4 Docking interaction between MCP-1 and Murrayamine-J

MCP-1		Murrayamine-J	Distance (A)	Docking energy (Kcal / mol)
Residue	**Atom**			
TYR13	N	O	2.7	-7.95
ASN14	N	O	3.0	
ASN17	N	C	3.6	

Table.5 Docking interactions between MCP-1 and Murrayanol

MCP-1		Murrayanol	Distance (A)	Docking energy (Kcal / mol)
Residue	**Atom**			
ASN-17	ND2	O	2.7	-6.9
CYS-52	N	O	3.0	

Table.6 Docking interactions between MCP-1 and Mahanine

MCP-1		Mahanine	Distance (A)	Docking energy (Kcal / mol)
Residue	**Atom**			
ARG30	NE	O	3.1	-7.55

Table.7 Overall docking results between MCP-1 and Carbazole alkaloids

COMPOUNDS	KEY RESIDUES	DOCKING ENERGY (Kcal / Mol)	NO.OF. HYDROGEN BONDS
Mahanimbilol	PRO-8, THR-10, THR-32, SER-33	-7.77	3
Murrayamine-M	ASN17, THR16	-7.99	2
Murrayamine-J	TYR13, ASN14	-7.95	2
Murrayanol	LYS44, GLU80	-6.9	3
Mahanine	ARG29, ARG30	-7.55	2

Fig.1 Crystal structure of the MCP-1

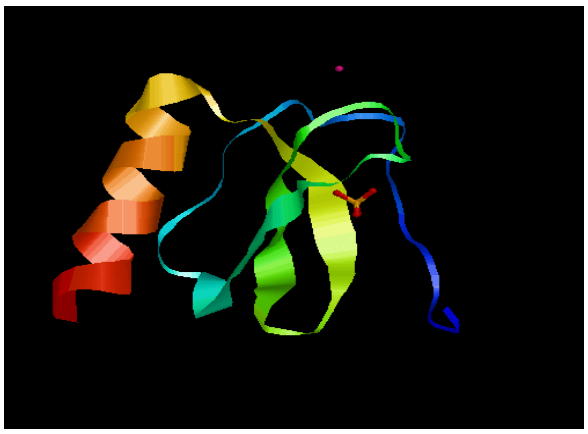
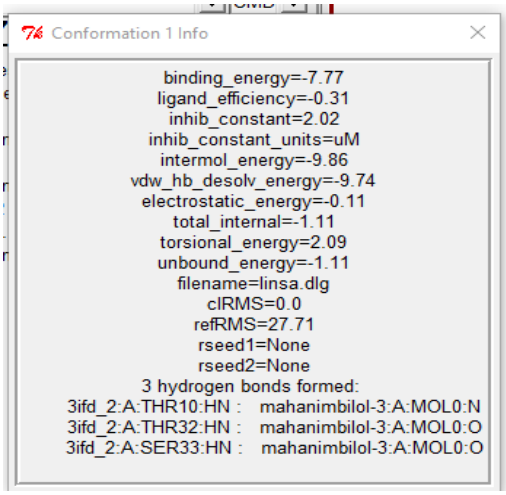
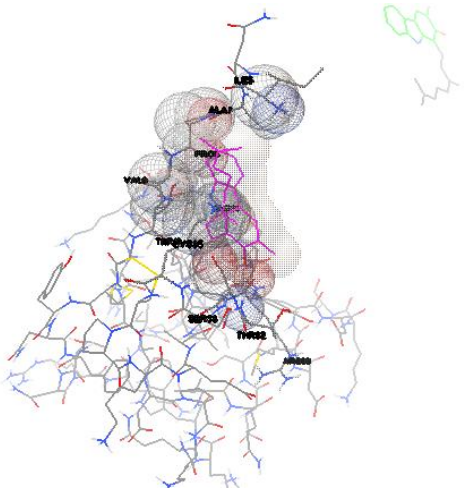


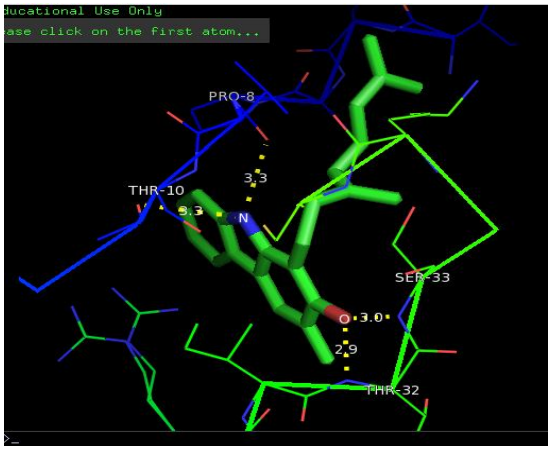
Fig.2 (a) Docking score; (b) Interactions between MCP-1 and Mahanimbilol visualized using Autodesk (c) Visualization of hydrogen interaction between MCP-1 and Mahanimbilol using PyMol



(a)

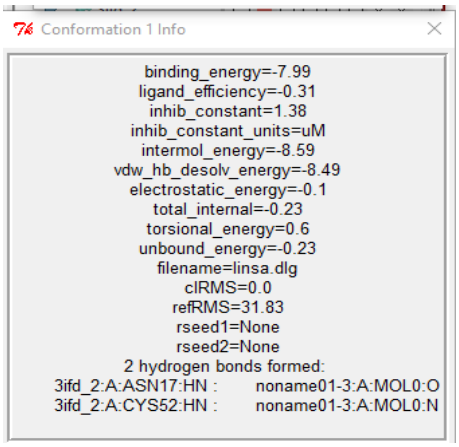


(b)

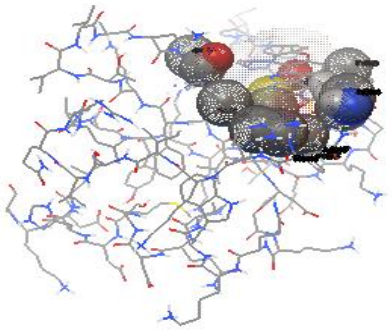


(c)

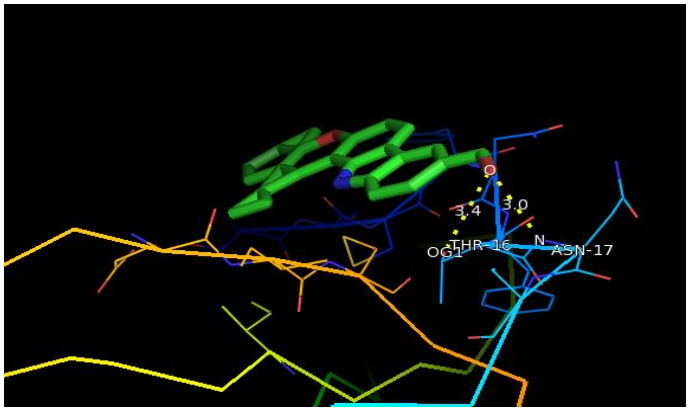
Fig.3 (a) Docking score; (b) Interaction between MCP-1 and Murrayamine-M visualized using Auto dock; (c) Visualization of hydrogen interaction between MCP-1 and Murrayamine-M



(a)

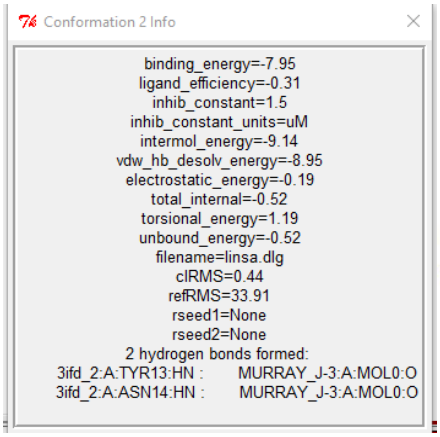


(b)

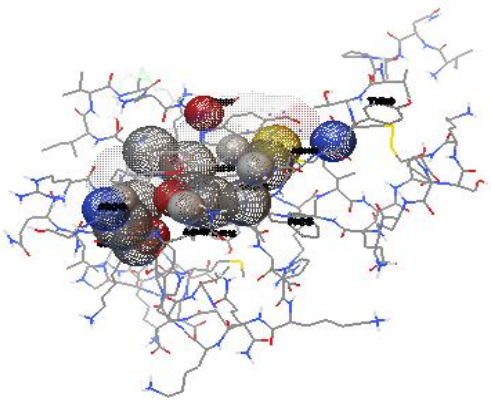


(c)

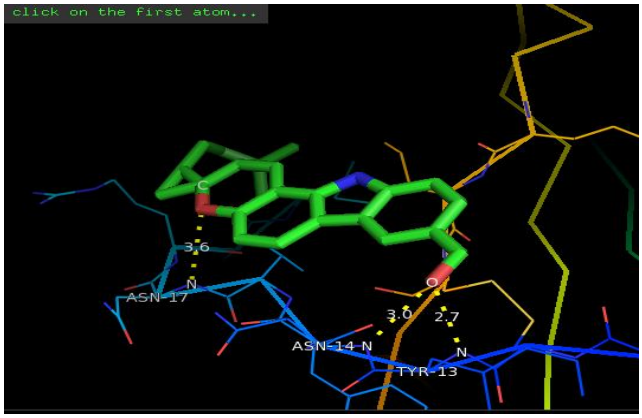
Fig.4 (a) Docking score (b) Interaction between MCP-1 and Murrayamine-J visualized using Auto dock (c) Visualization of hydrogen interaction between MCP-1 and Murrayamine-J using PyMol



(a)

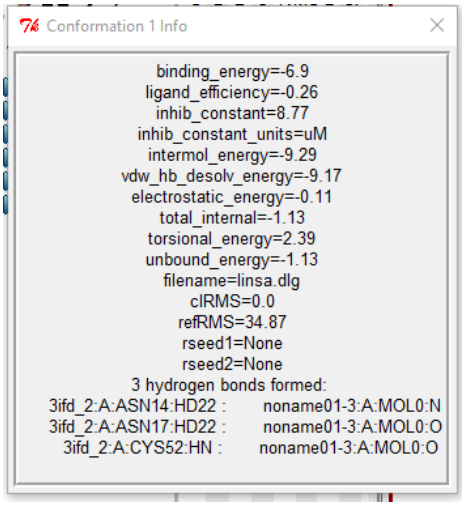


(b)

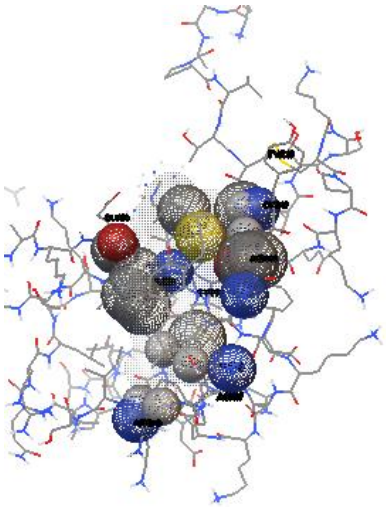


(c)

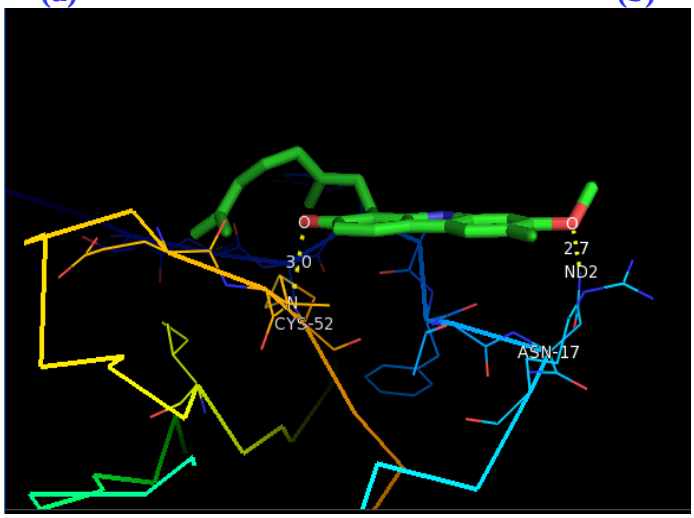
Fig.5 (a) Docking score; (b) Interaction between MCP-1 and Murrayanol visualized using Auto dock (c) Visualization of hydrogen interaction between MCP-1 and Murrayanol using PyMol



(a)

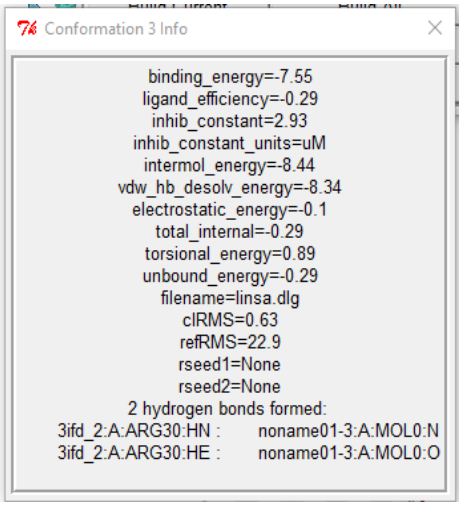


(b)

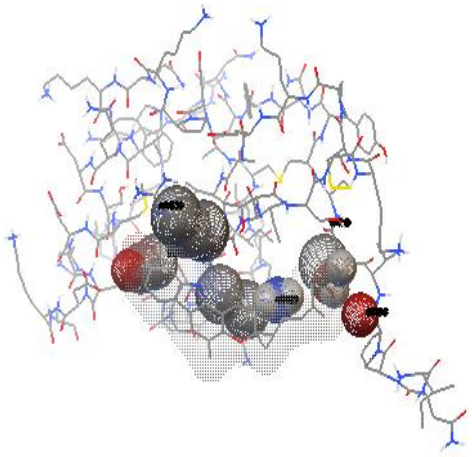


(c)

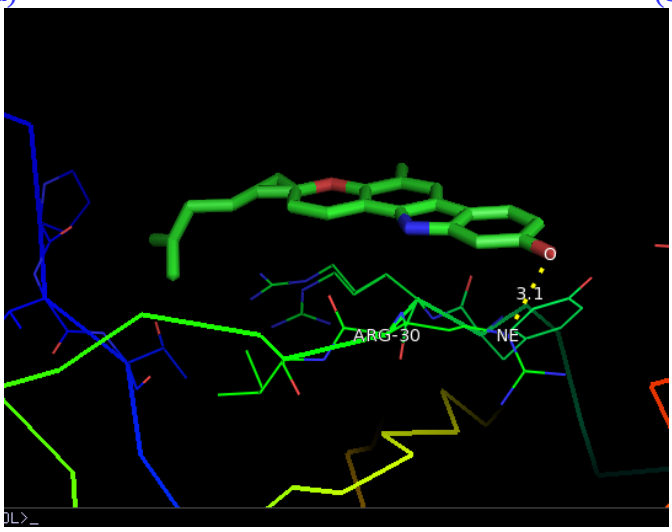
Fig.6 (a) Docking score; (b) Interactions between MCP-1 and Mahanine visualized using Auto dock (c) Visualization of hydrogen interactions between MCP-1 and Mahanine using PyMol.



(a)



(b)



(c)

Docking Analysis of Carbazole alkaloids against MCP-1

The 5 Carbazole alkaloids compounds (Mahanine, Mahanimbilol, Murrayanol, Murrayamine-M, and Murrayamine-J) were docked against MCP-1 receptor. The graphical user interface program "Auto-Dock Tools" was used to prepare, run, and analyze the docking simulations. Kollman united atom charges, solvation parameters and polar hydrogens were added into the receptor PDB file for the preparation of protein in docking simulation. Auto dock (Goodsell *et al.*, 1996, Jones G *et al.*, 1997, Rarey M *et al.*, 1996) requires precalculated grid maps, one for each atom type present in the flexible molecules being docked and it stores the energy arising from the interaction with rigid macromolecules. The grid box size was set at 126, 126, and 126 A^0 (x, y, and z) to include all the amino acid residues that present in rigid macro molecules. Auto grid 4 programs, supplied with Auto dock 4

was used to produce grid maps. The Lamarckian Genetic Algorithm (LGA) (Morris GM *et al.,* 1998) was chosen search for the best conformers. The best ligand-receptor structure from the docked structure was chosen based on the lowest energy and minimal solvent accessibility of the ligand. The carbazole alkaloids compounds (Mahanimbilol, Murrayamine-M, Murrayamine-J, Murrayanol, and Mahanine) and MCP-1 binding energy are shown in Figures 2a-6a, final conformation is shown in Figures 2b-6b, and the interactions visualization using PyMol shown in Figures 2c-6c. Hydrogen bond distance between the donor and acceptor atoms are shown in Tables 2-6.

The 5 carbazole alkaloid compounds (Mahanine, Murrayamine-M, Murrayanol, Murrayamine-J, and Mahanimbilol) from *Murraya koenigii* were docked against MCP-1 resulted in receptor and ligand complex. The docked structures were analyzed and the interactions were seen. Hydrogen bond interactions and the binding distance between the donors and acceptors were measured for the best conformers (Bharathi *et al.,* 2010). The binding energy is correlated with the probability of affinity and stable bound between ligand and its receptor.

Binding energy values may also predict the bioactivity value for ligands to the corresponding receptor (Kartasasmita *et al.,* 2009). The result of this study shows that the docking of MCP-1 (a) against Mahanimbilol and Murrayanol formed three hydrogen bonds each with the binding energy of -7.77 and -6.9 Kcal / mol; (b) against Murrayamine-M, Murrayamine-J, and Mahanine formed two hydrogen bonds with the binding energy of -7.99, -7.95 and -7.55 Kcal / mol, respectively. The overall results are summarized in Table 7.

The docking energy and the number of hydrogen bonds formed between the carbazole alkaloids and MCP-1 clearly indicates the enhanced activation of MCP-1.

Reducing the blood flow by activation of MCP-1 by carbazole alkaloids from *Murraya koenigii* offers a new therapeutic strategy to treat wounds. The 3D structure of Monocyte / Macrophage Chemoattractant protein-1 (MCP-1) is subjected to molecular docking with carbazole alkaloids from *Murraya koenigii*. Docking scores indicates the application of carbazole alkaloids as effective and natural therapeutic agents to combat wound. Enhancement of MCP-1 function by the carbazole alkaloids has the effect to provide the next generation wound healing therapeutics acting through a novel mechanism to truly modify the course of disease progression. Therefore, these results may offer therapeutic advantages in the treatment and prevention of wound.

References

Banu, M., *et al.,* In silico docking analysis of natural antioxidant from *Murraya koenigii* and Butylated Hydroxyanisole. *International journal of current research and academic review*. 3: 158-168 (2016).

Belperio J.A. *et al.,* CXC Chemokines in angiogenesis, 68 (1): 1-8 (2000).

Bharathi N, *et al.,* In silico docking analysis of curcumin an inhibitor for obesity, *Int J Pharma Bio Sci*, 1(4) ISSN: 0975-6299 (2010).

Clark RAF *et al.,* The molecular and cellular biology of wound repair, R.A.F. Clark, Ed, pp.3-50, plenum press, New York, 2nd edition (1996).

Dewald O *et al.,* CCL2 / Monocyte Chemoattractant protein-1 regulates inflammatory responses critical to

healing myocardial infarcts. Circ Res. 96 (8): 881-889 (2005).

Dhananjayan Karthik *et al.,* In silico docking analysis of dipeptidylpeptidase-4 (DDP-4 or CD26) with some selective bioflavonoids using genetic Lamarckian algorithm, *Journal of computational method in molecular design*.4 (2): 24-31 ISSN: 2231-3176 (2014).

Goodsell DS *et al.,* Automated docking of flexible ligands: applications of Autodock. J Mol recogn, 9 (1): 1-5, (1996).

Guo S. *et al.,* Factor affecting wound healing, *Journal of dental research featuring critical review in oral biology and medicine J dent res.* 89 (3): 219-229 (2010).

Helen *et al.,* The protein data bank: a historical perspective. Acta crystallography section A: foundation of crystallography, A64 (1): 88-95, (2008).

Helen M *et al.,* The protein data bank: a historical perspective. Acta Crystallography Section A: foundation of Crystallography, A64 (1):88-95 (2008).

http://accelrys.com/products/discoverystudio/structure-based-design.html (Accessed on November 21, 2014).

Jones G*et al.,* Development and validation of a genetic algorithm for flexible docking, *J Mol Biol,* 267:727-748, (1997).

Kartasasmita RE, *et al.,* Quercetion derivatives docking based on study of flavonoids interaction to cyclooxygenase-2. *Indones J Chem,* 9:297-302, (2009).

Morris GM, *et al.,* Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function, *J comput chem,* 19 (14): 1639-1662, (1998).

Rarey M, *et al.,* A fast-flexible docking method using an incremental construction algorithm, *J Mol Biol,* 261:470-89, (1996).

Sathish Kumar N *et al.,* In silico docking analysis of curcumin an inhibitor for obesity, *Int j pharma bio sci,* 1(4), ISSN: 0975-6299. (2010).

Shafia Mir *et al.,* Molecular docking: Approaches, Types, Application and Basic Challenge. *Journal of analytical and bio analytical techniques,* 8:356 ISSN: 2155-9872 (2017).

Syed Aun Muhammad *et al.,* In silico analysis and molecular docking studies of potential angiotensin-converting enzyme inhibitor using quercetin glycosides. *Pharmacognosy magazine* 11 (42): S123-S126 (2015).

TakaakiFujii *et al.,* Nonendothelial Mesenchymal Cell-Derived MCP-1 is required for FGF-2_ Mediated Therapeutic Neovascularization. 26: 2483-2489 (2006).

Wellstein A, *et al.,* Fibroblast growth factors, their receptors and signaling, *Endocr Relat Cancer.* 7 (3): 165-97 (2000).

How to cite this article:

Victoriya Salomi M., N. Vijayalakshmi, Linsa Santhosh and Vishwa Priya M. 2017. Prediction of Binding Affinity and Molecular Interaction of Mcp-1 with Carbazole Alkaloids from *Murraya koenigii*. *Int.J.Curr.Res.Aca.Rev.* Special Issue-4: 59-69.