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

Discovery of Potential Stat3 Activator from *Murraya koenigii* for Wound Healing

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KEYWORDS

Wound healing, Carbazole alkaloids, Murraya koenigii, Anti-inflammation, IL-10, STAT3, Molecular docking

A B S T R A C T

Murraya koenigii commonly known as curry plant belongs to the family Rutaceae. It is a medicinal plant which is native to India. The curry leaf is believed to have several pharmacological properties such as anti-diabetic, antioxidant, antimicrobial, anti-inflammatory, anticarcinogenic and hepato-protective activities. The plant is the rich source of carbazole alkaloids. The alkaloids obtained from naturally occurring sources have been the subject of extensive research, mainly because of their wide spread application in traditional medicine. Carbazole alkaloids from *Murraya koenigii* exibit wound healing properties. Wounds are injuries that break the skin or other body tissues, they include cuts, scarpes, scratches and punctured skin. Disruption of the integrity of skin, mucosal surfaces or organ tissue results in the formation of a wound. The process of wound repair requires a complex interplay of resident epithelial and mesenchyma cells with hematopoietic cells to accomplish the stages of wound healing. STAT-3 (Signal transducer and activator of transcription-3) is one of transcription factors, stimulated by IL-10. IL-10 is a 35-KDa homodimeric cytokine that is produced by a variety of cell types, including T-cells, monocytes and macrophages. It is known to be a major regulator in suppressing the inflammatory response. IL-10 binds to IL-10 R receptor and activates the STAT3 cascade, where phosphorylated STAT3 homodimers translocate to the nucleus within seconds to activate the expression of target genes. In the skin, karatinocytes have been shown to be capable of producing IL-10 after injury. Docking of various therapeutically important chemical entities to the specific target sites offers a meaningful strategy that may have tremendous scope in a drug design. The 3D structure of signal transducer and activator of transcriptor 3 (STAT3) is subjected to molecular docking with carbazole alkaloids from *Murraya koenigii*. The study indicates Bismahanine and Mukoeic acid exhibit least binding energy and hence they are considered as Potential and Natural Therapeutic agents to heal wound.

Introduction

Murraya koenigii, commonly known as *curry* leaf or *karipatta* in India, belongs to the Family Rutaceae, which represent more than 150 genera and 1600 species (Satyavati *et al.,* 1987). *Murraya koenigii*is more or less deciduous shrub or small tree reaching up to 6 m in height. The plant has a short trunk with 15-40 cm diameter with smooth, greyish or brown bark and has dense shady crown (Mhaskar *et al.,* 2000).Various parts of *Murraya koenigii* have been used in traditional or folk medicine for the treatment of rheumatism, traumatic injury and snake bite and it has been reported to have antioxidant, anti-diabetic, anti-dysenteric (Kong *et al.,* 1986; Keasri *et al.,* 2007), anti-tumour, anti-viral, anti-inflammatory, anti-convulsant, diuretic activities (Knolker and Reddy 2008).

The *Murraya* species are found to be richest source of carbazole alkaloids (Knolker and Reddy 2008). Alkaloids are a group of naturally occurring chemical compounds that contain mostly basic nitrogen atoms. Carbazole alkaloids have attracted much interest as synthetic targets since many of their derivatives exhibit broad range of potential biological activities. Wide variety of structurally diverse carbazole alkaloids with useful biological activities have been isolated from different natural sources over the past few decades (Ohira *et al.,* and Schmidt *et al.,* 2015).

Carbazole alkaloids are the major constituents of the *Murraya koenigii* and are known to possess cytotoxic, antioxidative, antimutagenic and anti-inflammatory activities (Adebajo *et al.,* 2006; Tachibana *et al.,* 2001; Ramsewak *et al.,* 1999). Biologically active carbazole alkaloids are also reported to have antimicrobial properties (Ramsewak *et al.,* 1999).

A wound is defined as damage or disruption to the normal anatomical structure and function (Robson *et al.,* 2001). This can range from a simple break in the epithelial integrity of the skin or it can be deeper, extending into subcutaneous tissue with damage to other structures such as tendons, muscles, vessels, nerves, parenchymal organs and even bone (Alonso *et al.,* 1996).Wound healing can be defined as the physiology by which the body replaces and restores function to damaged tissues (Tortora *et al.,* 1996).Wound healing is a complex physiological process that is dependent on a number of inter-related factors. Wound assessment and treatment should be based on an understanding of normal tissue repair and factors affecting the process (Flanagan *et al.,* 2000). All tissues in the body are capable of healing by one of two mechanisms: regeneration or repair. Regeneration is the replacement of damaged tissues by identical cells and is more limited than repair.

In humans, complete regeneration occurs in a limited number of cells or example, epithelial, liver and nerve cells. The main healing mechanism is repair where damaged tissue is replaced by connective tissue which then forms a scar.

The various processes of acute tissue repair, which are triggered by tissue injury, may be united into a sequence of four time-dependent phases: (i) coagulation and haemostasis, beginning immediately after injury; (ii) inflammation, which begins shortly thereafter; (iii) proliferation, which starts within days of the injury and encompasses the major healing processes; and (iv) wound remodelling, in which scar tissue formation takes place, and which may last up to a year or more (Vanwijck *et al.,* 2001; Degreef *et al.,* 1998; Broughton *et al.,* 2006; Hunt *et al.,* 2000).

Interleukin (IL)-10 is the most important cytokine with anti-inflammatory properties (Sabat *et al.,* 2010). The gene encoding human IL-10 is located on chromosome 1 covering a total of 5.1 kb pairs comprising five exons (Kim *et al.,* 1992). Human IL-10 is a 35 kDa homodimer that is composed of two, non-covalently bonded monomers. The homodimer has two V-oriented domains, each of which is composed of six helices: four (A-D) of one monomer and two (E' and F') of the other. Within the monomer, two disulfide bridges exist (C30-C126 and C80-C132) that are essential for maintaining the structure and the biological activity of the cytokine (Windsor *et al.,* 1993). IL-10´s pleiotropic activities are mediated by a specific cell surface receptor complex. The IL-10 receptor (IL-10R) is composed of two different chains, IL-10R1 and IL-10R2 (Kotenko *et al.,* 2002). Interleukin 10 (IL-10) is a potent anti-inflammatory cytokine that plays a crucial, and often essential, role in preventing inflammatory and autoimmune pathologies (Sabat *et al.,* 2010 Oct; Kuhn *et al.,* 1993). Based on its immune modulating functions, IL-10 has been considered an attractive candidate for therapeutic applications for treatment of acute and chronic inflammation, autoimmunity, cancer and infectious disease (Asadullah *et al.,* 2003). In the skin, keratinocytes have been shown to be capable of producing IL-10 after injury (An *et al.,* 2010).

Signal transducer and activator of transcription-3 (STAT-3) is one of six members of a family of transcription factors. The STAT protein family was discovered in the course of studies of signalling specificity from IFN receptors (Bharat *et al.,* 2009 August).

In anti-inflammatory response, IL-10 binding to IL-10R activates the STAT3 cascade, where phosphorylated STAT3 homodimers translocate to the nucleus within seconds to activate the expression of target genes. Most importantly, both IL-10 and STAT3 are essential for the anti-inflammatory response and cannot be replaced by any other cytokine or transcription factor (TF), when STAT3 is stimulated by IL-10, STAT3 is anti-inflammatory (Murray 2006).

In silico docking studies will provide a high-quality interaction between the ligand and receptor. This approach is now time-consuming, reasonable; minimize the cost and side effects when entered into clinical studies (Gurudeeban *et al.,* 2012).

Molecular Docking is a method which anticipates the favored orientation of ligand against receptor (Protein) to make a stable complex (Lengauer and Rarey 1996).

Docking studies were performed with STAT3 proteins and carbazole alkaloids using the automated docking tool, AutoDock 4.2.3. Autodock results were analyzed based on the interactions between STAT3 protein and compounds. A search algorithm which tabulates the energy of the possible orientation is used to study the various parameters of docking.

Materials and Methods

Protein preparation

Three-dimensional structure of STAT3 protein (PDB ID: 5UG9) was retrieved from the Uniprot database. The structure visualized using the molecular graphics program PyMol® intended for the structural visualization of proteins. For docking simulations, the hetero atoms were removed, and H-atoms were added into protein structure using the automated docking tool, AutoDock.

Preparation of ligand

3D structure of carbazole alkaloids from *Murraya koenigii* was retrieved from the PubChem® database. The 2D structures of the compound were drawn and edited using Chemsketch version 12.0. The downloaded structures were converted into pdb format using freely available open source tool, Open Babel (Geldenhuys *et al.,* 2006) and The SMILES format for all the compounds was generated using Open Babel version 2.3.1 (O'Boyle *et al.,* 2011).

In silico docking

Molecular docking is an attractive scaffold to understand drug biomolecular interactions for the rational drug design and discovery, as well as in the mechanistic study by placing a molecule (ligand) into the preferred binding site of the target specific region of the DNA/protein (receptor) mainly in a non-covalent fashion to form a stable complex of potential efficacy and more specificity (Rohs *et al.,* 2005; Guedes *et al.,* 2014).

Results and Discussion

Sequence retrieval: STAT3

The sequence of Signal transducer and activator of transcription-3 (STAT3) is retrieved from uniprot database and sequence accession number is P00533-1**.**

Structure retrieval

Three dimensional structure (Crystal structure) of the STAT3 is retrieved from Uniprot database and its PDB ID is 5UG9. Three dimensional structure is visualized using RasMol.

Preparation of ligands

For docking analysis 7 carbazole alkaloids from *Muraya Koenigii* was selected. The structures of Mukoeic acid, Euchrestine, Isomahanine, Bismahanine, Murrayanol, Phebalosin and Murrayacine was retrieved from the Pubchem compound database from the National Center for Biotechnology Information. The two-dimensional structures of the ligands were generated using the ACD/ChemSketch tool.

This software contains tools for 2D cleaning, 3D optimization, and viewing. These data are saved as a molecular format file (MDL MOL format). The molecular format 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 koeniji* is shown in Table 1.

Fig.1 *Murraya koenigii*

Fig.2 Schematic representation of IL-10 interaction with STAT3

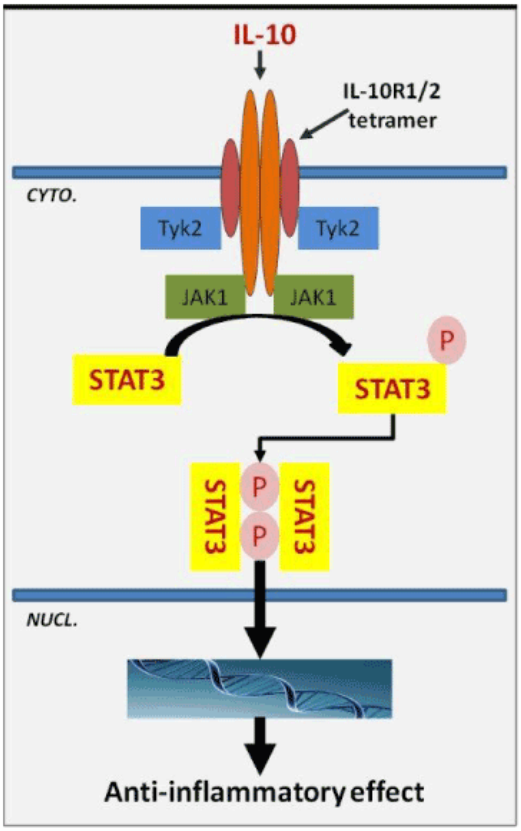


Fig.3 Crystal structure of the STAT3

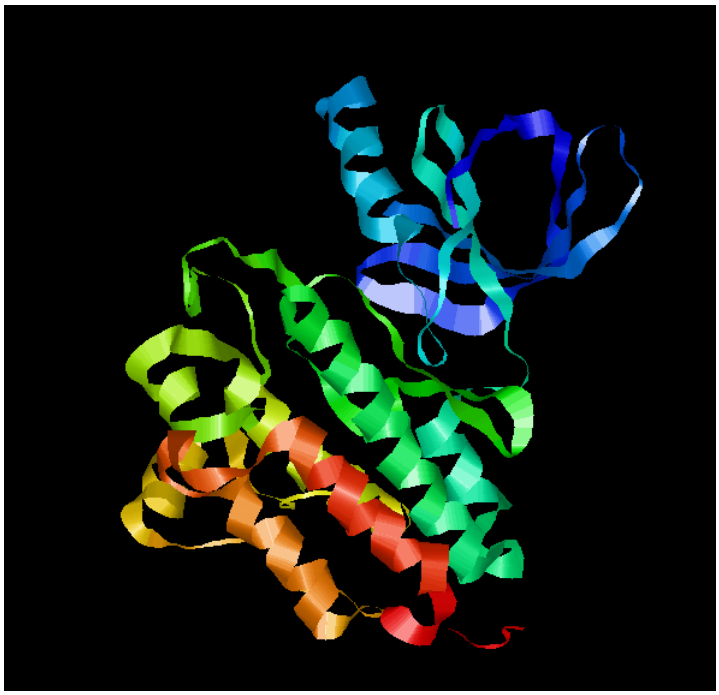
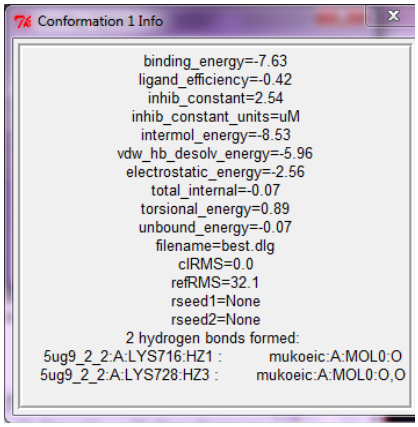
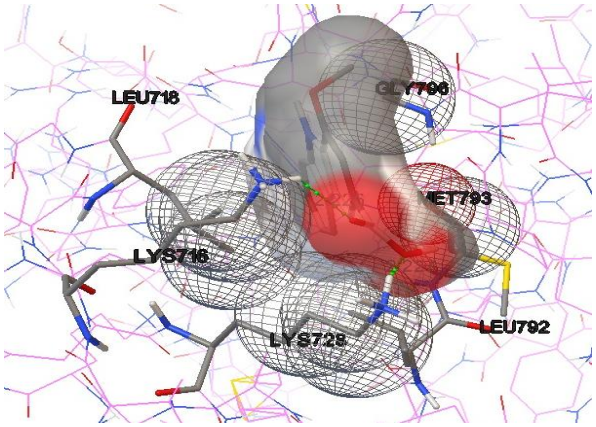


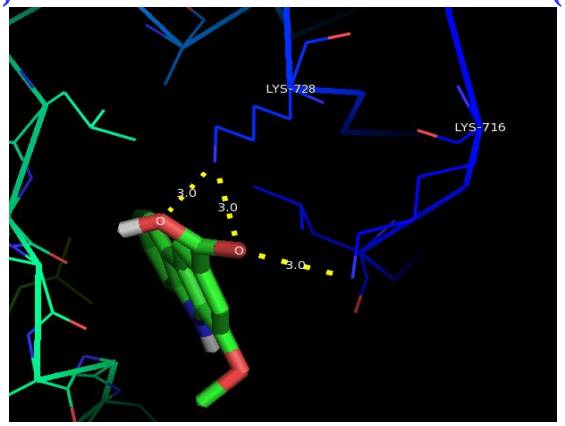
Fig.4 (a) Docking score; (b) Interactions between STAT3 and Mukoeic acid visualized using Autodock; and (c) Visualization of hydrogen interactions between STAT3 and Euchrestine using PyMol (yellow colour dotted lines represent hydrogen bond)



(a)

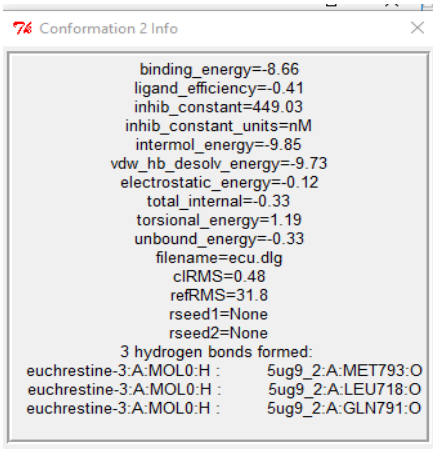


(b)

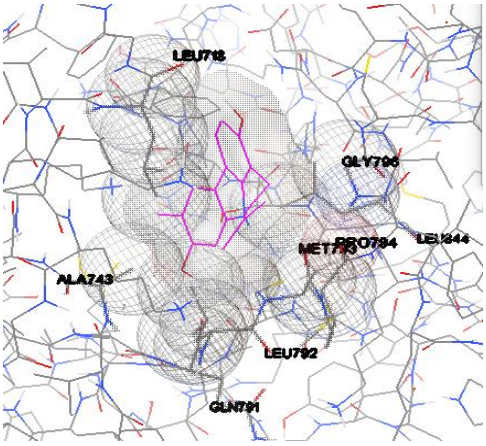


(c)

Fig.5 (a) Docking score; (b) Interactions between STAT3 and Euchrestine visualized using Autodock; and (c) Visualization of hydrogen interactions between STAT3 and Euchrestine using PyMol (yellow colour dotted lines represent hydrogen bond)



(a)



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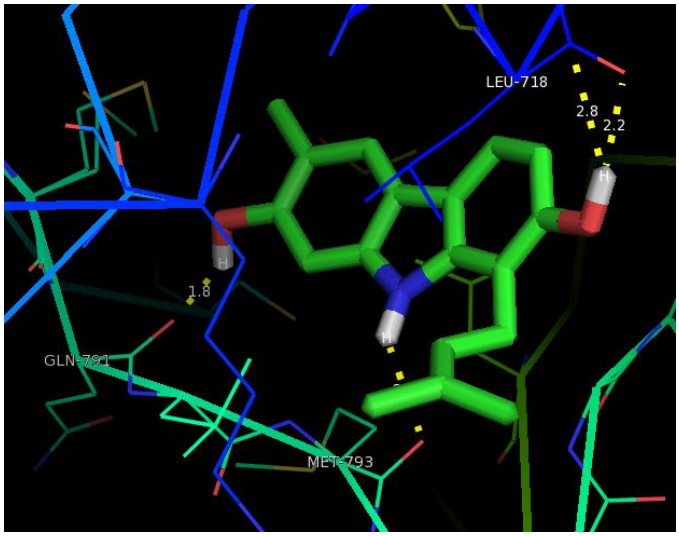
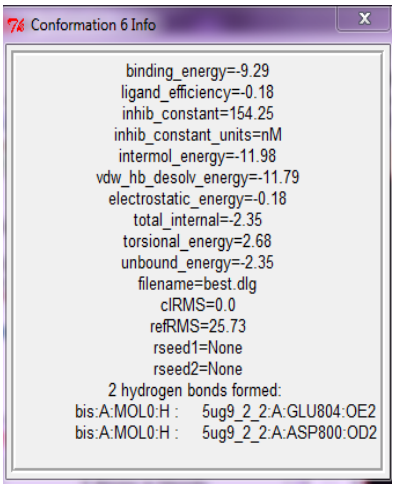
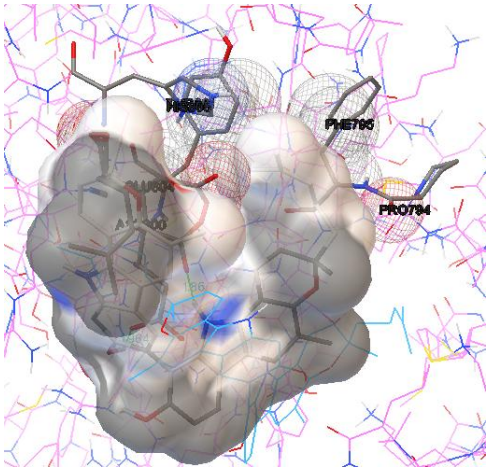


(c)

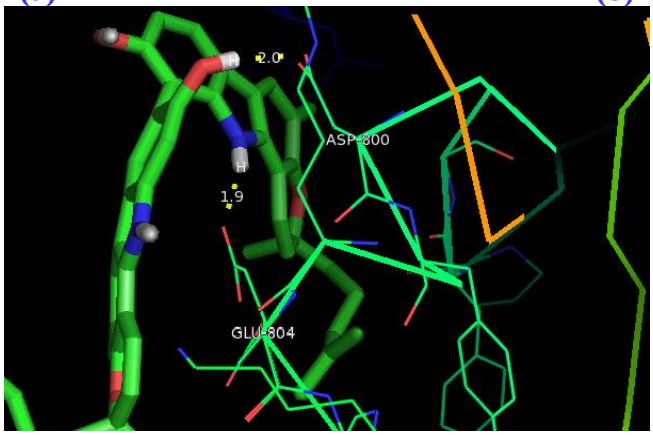
Fig.6 (a) Docking score; (b) Interactions between STAT3 and Bismahanine visualized using Autodock; and (c) Visualization of hydrogen interactions between STAT3 and Bismahanine using PyMol (yellow colour dotted lines represent hydrogen bond)



(a)

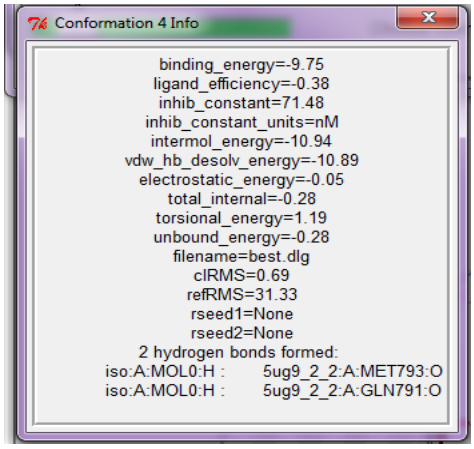


(b)

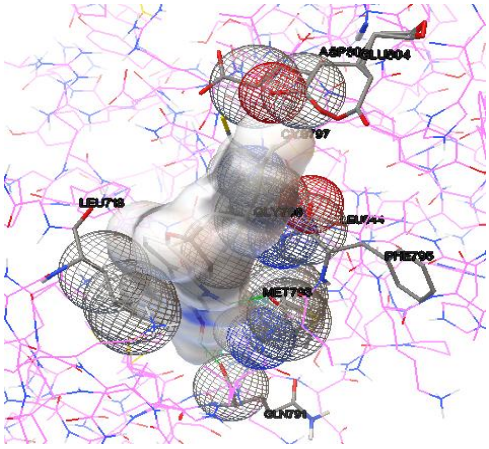


(c)

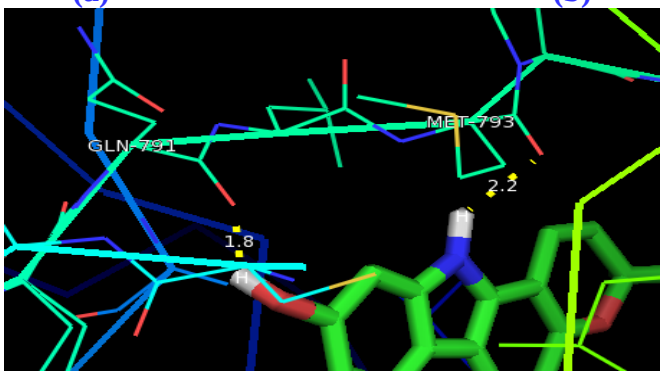
Fig.7 (a) Docking score; (b) Interactions between STAT3 and Isomahanine visualized using Autodock; and (c) Visualization of hydrogen interactions between STAT3 and Isomahanine using PyMol (yellow colour dotted lines represent hydrogen bond)



(a)

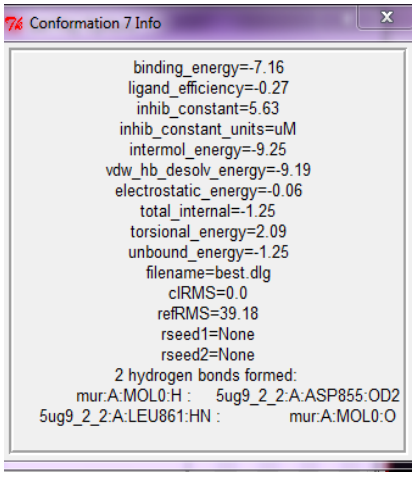


(b)

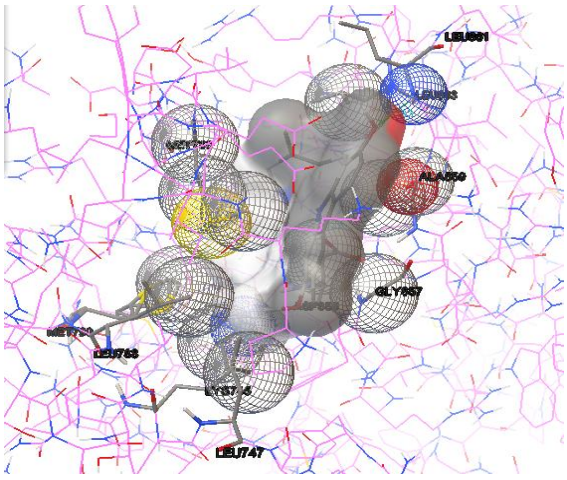


(c)

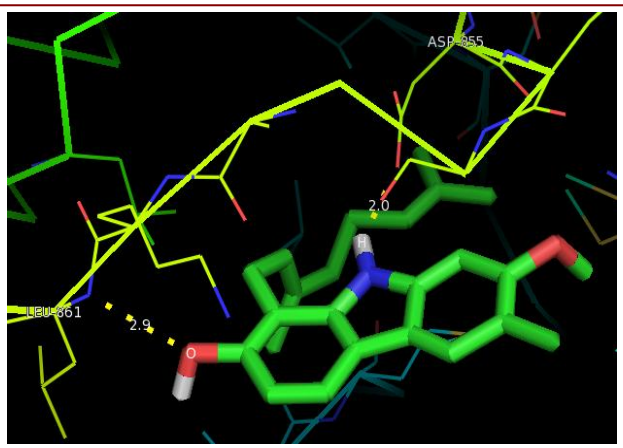
Fig.8 (a) Docking score; (b) Interactions between STAT3 and Murrayanol visualized using Autodock; and (c) Visualization of hydrogen interactions between STAT3andMurrayanolusingPyMol (yellow colour dotted lines represent hydrogen bond)



(a)

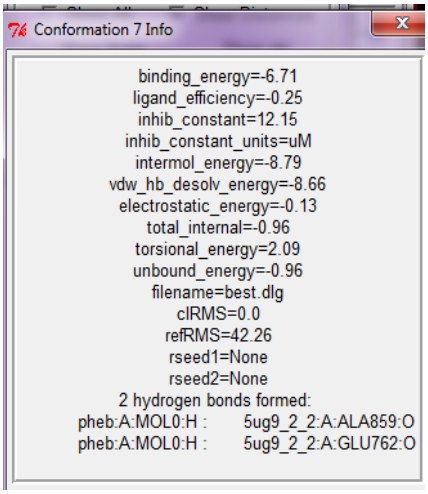


(b)

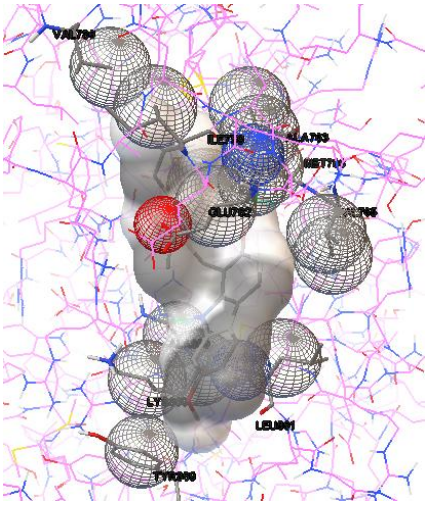


(c)

Fig.9 (a) Docking score; (b) Interactions between STAT3 and Phebalosin visualized using Autodock; and (c) Visualization of hydrogen interactions between STAT3 and Phebalosin using PyMol (yellow colour dotted lines represent hydrogen bond)



(a)



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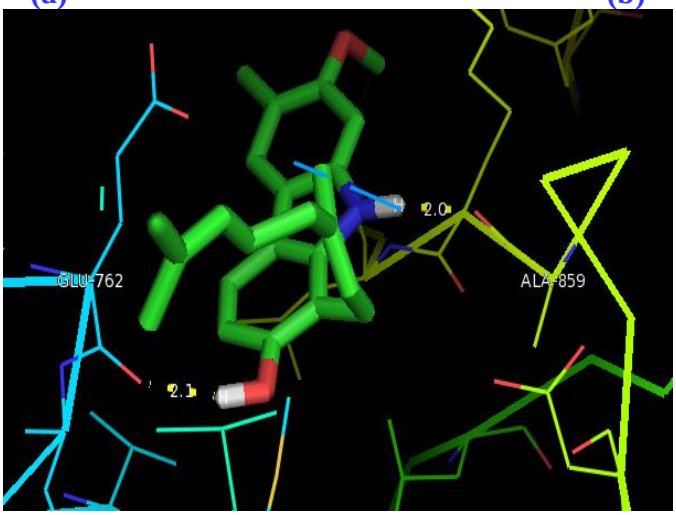
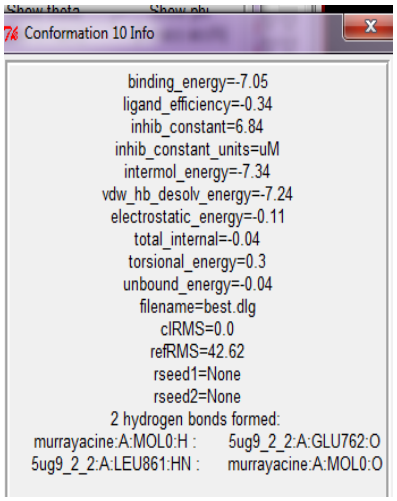
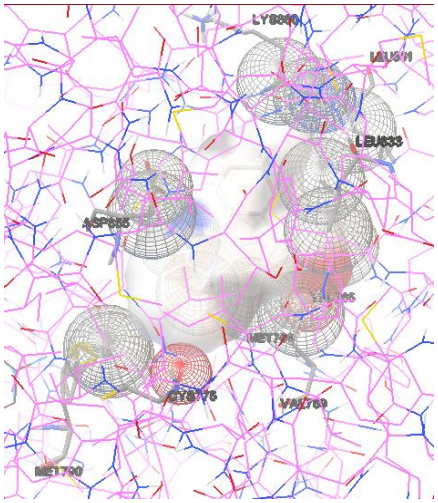


(c)

Fig.10 (a) Docking score; (b) Interactions between STAT3 and Murrayacine visualized using Autodock; and (c) Visualization of hydrogen interactions between STAT3 and Phebalosin using PyMol (yellow colour dotted lines represent hydrogen bond).



(a)



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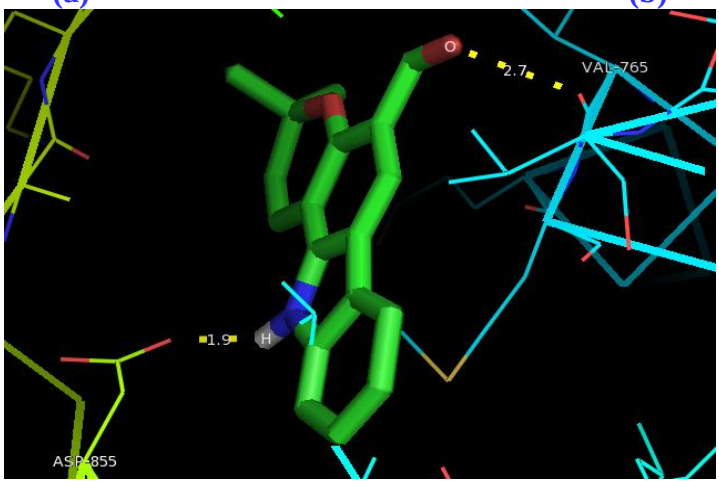
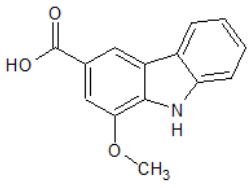
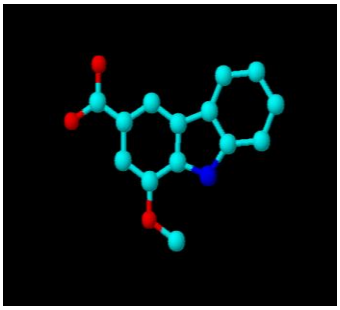


(c)

Table.1 Compounds extracted from *Murraya koeniji*

S.No	COMPOUNDS	2D-STRUCTURE	3D-STRUCTURE
1.	Mukoeic acid		

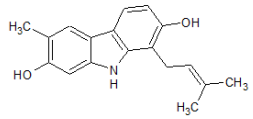
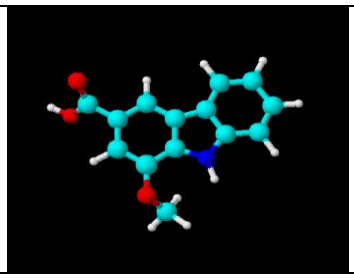
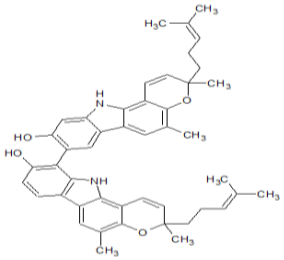
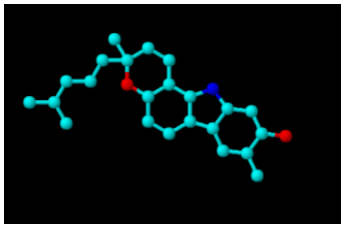
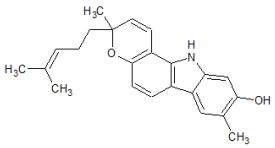
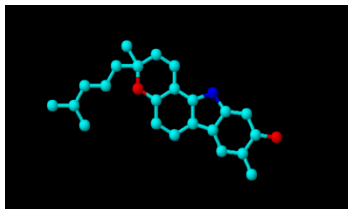
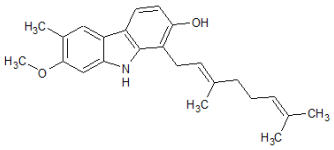
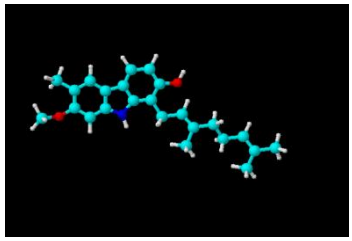
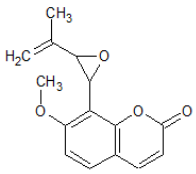
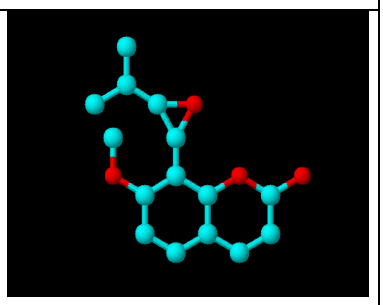
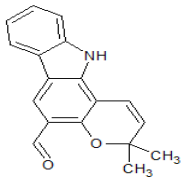
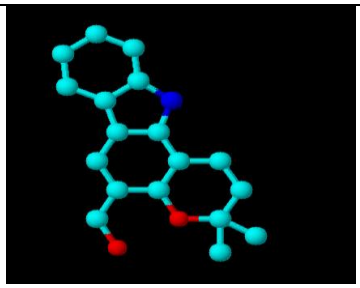
2.	Euchrestine		
3.	Bismahanine		
4.	Isomahanine		
5.	Murrayanol		
6.	Phebalosin		
7.	Murrayacine		

Table.2 Docking interactions between STAT3 and Mukoeic acid

STAT3		Mukoeic acid	Distance (Å)	Docking energy
Residue	**Atom**			
LYS716	HZ1	O	3.o	-7.63
LYS728	HZ3	O	3.0	

Table.3 Docking interactions between STAT3 and Euchrestine

STAT3		Euchrestine	Distance (Å)	Docking energy
Residue	**Atom**			
GLN791	O	H	1.8	-8.66
LUE718	O	H	2.8,2.2	
MET793	O	H	2.4	

Table.4 Docking interactions between STAT3 and Bismahanine

STAT3		Bismahanine	Distance (Å)	Docking energy
Residue	**Atom**			
GLU804	OE2	H	1.9	-9.29
ASP800	OD2	H	2.0	

Table.5 Docking interactions between STAT3 and Isomahanine

STAT3		Isomahanine	Distance (Å)	Docking energy
Residue	**Atom**			
MET753	O	H	**2.2**	**-9.25**
GLN791	O	H	**1.8**	

Table.6 Docking interactions between STAT3 and Murrayanol

STAT3		Murrayanol	Distance (Å)	Docking energy
Residue	**Atom**			
ALA859	OD2	H	2.0	-7.16
LEU816	HN	O	2.9	

Table.7 Docking interactions between STAT3 and Phebalosin

STAT3		Phebalosin	Distance (Å)	Docking energy
Residue	**Atom**			
ALA859	O	H	2.0	-6.71
GLU762	O	H	2.1	

Table.8 Docking interactions between STAT3 and Murrayacine

STAT3		Murrayacine	Distance (Å)	Docking energy
Residue	**Atom**			
ASP855	O	H	1.9	-7.05
VAL765	HN	O	2.7	

Table.9 Overall docking results between STAT3 and carbazole alkaloids

Compounds	Key Residues	Docking energy (Kcal/Mol)	No. of Hydrogen bonds
Mukoeic acid	LYS716, LYS728	-7.63	2
Euchrestine	GLN791, LUE718, MET793	-8.66	3
Bismahanine	GLU804, ASP800	-9.29	2
Isomahanine	MET753, GLN791	-9.25	2
Murrayanol	ALA859, LEU816	-7.16	2
Phebalosin	ALA859, GLU762	-6.71	2
Murrayacine	ASP855, VAL765	-7.05	2

Docking Analysis of Carbazole alkaloids against STAT3

The 7 Carbazole alkaloids compounds (Mukoeic acid, Euchrestine, Isomahanine, Bismahanine, Murrayanol, Phebalosin and Murrayacine) are docked against STAT3 receptor. Molecular docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex (Lengauer and Rarey 1996). Docking plays an important role in the rational design of drugs (Kitchen *et al.*, 2004). Docking studies were performed with STAT3 proteins and seven carbazole alkaloids using the automated docking tool, AutoDock 4.2.3. MGL (Molecular Graphics Laboratory) Tools of AutoDock used to create PDBQT files from traditional PDB files. The receptor file prepared with the addition of polar hydrogens, Kollman charges, and solvation parameters. This tool operates using a Lamarckian genetic algorithm (LGA) (Morris *et al.*, 1998). The active sites were input and a grid parameter file for each protein was generated by fixing the number of grid points on the x, y, and z axes to 126× 126 × 126, though the size changed depending on the amino acid residues that present in the receptor. The population size was set to 150 and the individuals were initialized randomly. Other docking parameters were set to the software's default values. The Lamarckian genetic algorithm was chosen to determine the best conformers in fifty independent trials of each carbazole alkaloids. The AutoGrid 4.2.3 and AutoDock 4.2.3 programs were used to produce grid maps and to obtain results. Then the file was saved as dpf file format.The docking used to retained the interaction between protein and ligand information For each interaction of protein and compound its shows maximum 10 conformations were obtained. The best ligand-receptor structure from the docked structures was chosen based on the lowest energy and minimal solvent accessibility of the ligand.

The 7 carbazole alkaloid compounds (Mukoeic acid, Euchrestine, Isomahanine, Bismahanine, Murrayanol, Phebalosin and

Murrayacine) from *Murraya koenigii* docked against STAT3 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 (Archana *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 a ligand to the corresponding receptor (Kartasasmita *et al.,* 2009). The result of this study shows that the docking of STAT3 (a) against Mukoeic acid formed two hydrogen bonds each with the binding energy of -7.63 Kcal/mol; (b) against Euchrestine formed three hydrogen bonds each with the binding energy of -8.66 Kcal/mol; (c) against Bismahanine formed two hydrogen bonds each with the binding energy of -9.29 Kcal/mol; (d) against Isomahanine formed two hydrogen bonds each with the binding energy of -9.25 Kcal/mol; (e) against Murrayanol formed two hydrogen bonds each with the binding energy of -7.16 Kcal/mol; (f) against Phebalosin formed two hydrogen bonds each with the binding energy of -6.71 Kcal/mol; (g) against Murrayacine formed two hydrogen bonds each with the binding energy of -7.05 Kcal/mol. The overall results are summarized in Table 8.

The docking energy and the number of hydrogen bonds formed between the carbazole alkaloids and STAT3 clearly indicates the enhanced activation of STAT3. The activation of STAT3 in turn increases the wound healing activity.

From the molecular docking studies with carbazole alkaloids of *Murraya koenigii*, docking scores indicated the application of carbazole alkaloids as Potential and Natural therapeutic agents to combat wounds. Enhancement of STAT3 function by the carbazole alkaloids has the potential to provide the next generation of wound healing therapeutics acting through a novel mechanism to truly modify the course of wound healing. Therefore, these results may offer therapeutic advantages in the treatment and prevention of wounds.

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How to cite this article:

Victoriya Salomi M., N. Vijayalakshmi and Ananthi M. 2017. Discovery of Potential Stat3 Activator from *Murraya koenigii* for Wound Healing. *Int.J.Curr.Res.Aca.Rev.* Special Issue-4: 70-85.