British Journal of Pharmaceutical Research
10(3): 1-7, 2016, Article no.BJPR.23792
ISSN: 2231-2919, NLM ID: 101631759

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Molecular Docking Studies of Sesquiterpenoids against *Helicobacter pylori* Peptide Deformylase

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SAM and NF designed the study, wrote the protocol. Authors MD and SAM managed the experimental process. Author AM wrote the first draft of the manuscript. Authors SR and IS managed the literature searches. Authors QM and NF prepare final draft of paper. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJPR/2016/23792
Editor(s):
(1) Syed A. A. Rizvi, Department of Pharmaceutical Sciences, College of Pharmacy, Nova Southeastern University, USA.
Reviewers:
(1) Alba E. Vega, Universidad Nacional de San Luis, Argentina.
(2) Anonymous, Erzincan University, Turkey.
(3) Nagahito Saito, Nemuro City Hospital, Nemuro, Japan.
Complete Peer review History: http://sciencedomain.org/review-history/13273

Short Research Article

Received 22nd December 2015
Accepted 28th January 2016
Published 11th February 2016

ABSTRACT

Helicobacter pylori is a gastric mucosal pathogen and is a major causative factor for gastrointestinal diseases like peptic ulcer and gastric cancer. New molecules are required for effective treatment due to emerging issues of antibiotic resistance. However, the recognition of anti-*Helicobacter pylori* agent is a difficult task due to inadequacy of perfect protein target sites. Peptide deformylase is a significant and essential enzyme for bacterial growth due to its vital role in peptide chain elongation. In human cells peptide deformylase has no effect on the synthesis of protein therefore it can be an effective and selective drug target against *Helicobacter pylori* infections. In this study, binding mode of five sesquiterpenoids against the peptide deformylase was determined. The 3-dimensional structure of peptide deformylase for *in-sillico* study was accessed from the Protein Data Bank. Pharmacokinetics profile of sesquiterpenoids derivatives

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was determined by applying Lipinski's rule of 5. The binding energies of molecular docking for 1 to 5 ligands are: -13, -15, -11, -13, and -11 kcal/mol respectively. The compound 2 exhibited reasonably good binding affinity (-15 kcal/mol) when compared with other ligands. This study could pave the ways for *in-vitro* analysis to establish these compounds as potential anti-*Helicobacter pylori* drugs.

Keywords: Helicobacter pylori; peptide deformylase; sesquiterpenoids.

1. INTRODUCTION

Helicobacter pylori is a gram-negative bacterium which is associated with various gastrointestinal abnormalities including peptic ulcer, gastric cancer [1,2] and gastric lymphoma [3,4]. Combination therapies with two or three antibiotics (e.g., clarithromycin, amoxicillin, or tetracycline) and one proton pump inhibitor (e.g., omeprazole) have been utilized to treat *H. pylori* infection [5]. However, eradication of *H. pylori* is not easy with existing therapies. *H. pylori* has a potential to develop resistance therefore the multiple therapy regimes have not been efficacious. Furthermore, this treatment may destroy the natural flora in the gastrointestinal tract, leading to side effects [6]. Thus, it is an urgent need to explore novel anti-*H. pylori* agents. Mostly, random screening with minimal inhibitory concentration assays like agar dilution and broth dilution methods were used to discover current anti *H. pylori* agents due to devoid of mature protein targets for screening. Consequently, for development of new drugs against this pathogenic bacterium requires exploring new molecular targets [7,8].

Peptide deformylase is considered an emerging molecular target against *H. pylori* which is involved in bacterial growth and protein synthesis. The synthesis of protein is induced with N-formylmethionylt-RNAi in both prokaryotic and eukaryotic cell organelles (e.g., chloroplast and mitochondria) that results into N-terminus expression of all new polypeptides. A formyl group of N-terminus is removed by catalytic activity of peptide deformylase during polypeptide chain elongation. Therefore, peptide deformylase is significant for growth of bacterial cell and its inhibition will produces anti-*H. pylori* activity [9]. Peptide deformylase is also present in human body [10,11]. In human cells peptide deformylase has no effect on the synthesis of protein and can be considered as selective target against *H. pylori* for drug development [12]. Therefore there is an ample scope to propose peptide deformylase inhibitors to develop new set of molecules with higher specificity. Many scientists have been working to synthesis or isolate potential compounds from natural sources.

Recently clinical setting has been revolutionized by many natural products and its synthetic derivatives in all therapeutic areas. Secondary metabolites of plants and microorganisms serve as lead compounds in development of new therapeutic drugs against infectious diseases and cancer. There are various classes of secondary metabolites (alkaloids, terpenoids, phenolics and glycosides) have been studied for their medicinal potential. Among secondary metabolites terpene and their derivatives (sesquiterpenoids) possess broad range of therapeutic activities [13]. Sesquiterpenoids have been reported for molluscicidal, antimicrobial, antiulcer, antileishmanial, antitumor, antiulcer, antimalarial and antimycobactarial activities [14,15]. Therefore in current study five previously reported sesquiterpenoids were used for docking studies against selective molecular target peptide deformylase (Fig. 1). Our study could pave the ways to discover new lead compounds and molecular targets against *H. pylori*.

2. MATERIALS AND METHODS

2.1 Target Protein Accession

The 3D structure of peptide deformylase was obtained from the Protein Data Bank (PDB ID: 2EW5) [16]. Peptide deformylase is significant for growth of bacterial cell and is an effective biological target against *H. pylori* infection.

2.2 Accession of Sesquiterpenoids Derivatives

The chemical structure of sesquiterpenoids, mukaadial, muzigadial, ugendensidial, ugandensolide and warburganal were incurred from PubChem database. Chem Bio-Draw and MOL2 file format were used to design these structures. Before transfering onto ArgusLab programming configuration of these ligands was ransformed to PDB format using Open Babel tool.

2.3 Ligands and Target Optimization

Optimization of ligand molecules and structural coordinates of the target protein was carried out by ArgusLab software for docking analysis [17]. Optimization leads to stable conformation of coordinates with minimum energy.

2.4 Analysis of Target Active Binding Sites

Proteins carry out their functions through interactions with other proteins and hence precisely recognizing the protein-ligand binding site assumes an essential part in protein functional annotation for drug discovery. The coordinates which are active sites of ligand in the target protein and these dynamic binding sites of target protein were investigated [18] using the DoGSite Scorer: Active Site Prediction and Analysis Server [19].

2.5 Molecular Docking Analysis

In sillico drug designing approach was applied to analyze structural complexes. Molecular docking was carried out by ArgusLab software [20]. Atomic affinity potentials computed on a grid was used to calculate the energy of interaction of ligand and protein as each step of simulation. The rest of the parameters were set as default.

2.6 Lipinski's Rule of 5

Pharmacokinetics properties (ADME/T) of selected compounds were determined by applying Cheminformatic Molinspiration tool of Lipinski's rule of 5 (RO5) [21]. According to the RO5, the molecules must have hydrogen bond acceptors ≤10 (N and O atoms), hydrogen bond donor's ≤5 (OH and NH groups), molecular weight <500 Da, and log P coefficient (Clog P) less than 5.

3. RESULTS AND DISCUSSION

Numerous technologies such as bioinformatics analysis or molecular docking, genomics and proteomics for addressing drug targets have been developed recently [22]. Molecular docking involved prediction of preferred orientation of one molecule with reference to other or to form stable complex. The interactions between biologically relevant molecules play a central role in signal transduction with in the living systems. Therefore molecular docking studies have been used to predict the binding orientation of small molecules or drug candidates to their protein targets to determine affinity and activity of the small molecule. Hence docking is a pharmaceutically significant technique that plays an important role in the rational drug design [23]. Furthermore, a reliable energy evaluation can easily indicate the quality of receptor-ligand putative complex and provide insights for biomedical science and drug development [24].

Therefore in this study, we have investigated sesquiterpenoids (Fig. 1) as inhibitors of peptide deformylase, which is essential for growth of *H. pylori* but not required by the mammalian cells [25]. Therefore different parameters have been studied to evaluate their biological potential by using docking methods. One of the most important parameter integrated with drug discovery or designing is pharmacokinetics (absorption, distribution, metabolism, and excretion) of drug leads [26].

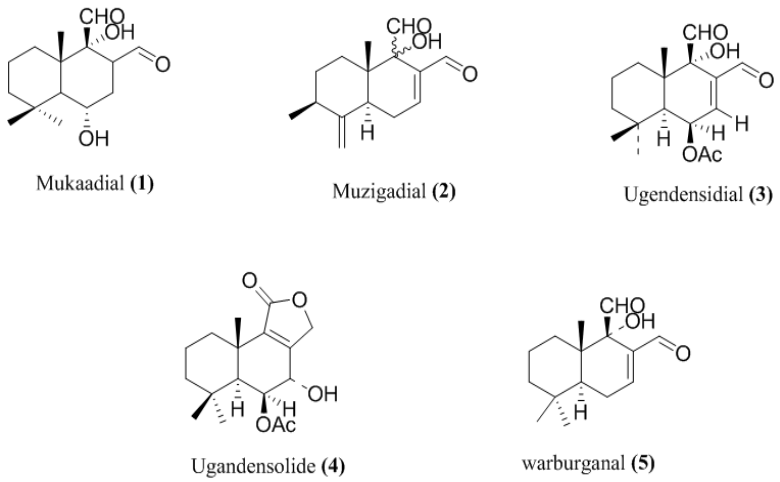

Fig. 1. Sesquiterpenoids used for docking against *Helicobacter pylori* Peptide deformylase

Recently computational methods have been developed to determine pharmacokinetic parameters [27]. The pharmacokinetic profile of these compounds showed that they have suitable drug likeness properties including absorption coefficient, total polarity of surface area, and volume (Fig. 2).

Crystal structure of peptide deformylase indicates it as a suitable target of compounds 1 to 5. The overall structure of *H. pylori* peptide deformylase folded in a similar way to the other peptide deformylases, and a cobalt ion tetrahedrally coordinated with two histidines, one cystine, and a water molecule (Fig. 3). The CD loop of *H. pylori* peptide deformylase adopted a different conformation as compared to other peptide deformylases implying that the selective *H. pylori* peptide deformylase inhibitors could be designed (Fig. 4).

The minimum binding energy indicated that the target enzyme was successfully docked with ligands molecules (Fig. 5). The AutoGrid model exhibited the most energetically positive binding mode of Compound 4 to enzyme site (Fig. 4). The sesquiterpenoids as ligands are docked into the produced consolidated matrices and the RMSD from native pose and the binding energies are assessed and it is observed that the weight averaged grids performed the best. The ligands demonstrated the best interaction with target proteins in light of the RMSD values.

Compound 2 showed relatively good binding affinity (-15 kcal/mol) as compared to other ligand. The docking of enzyme target focus with ligands utilizing docking methodology uncovered that all the computationally predicted lowest energy complexes of enzyme are stabilized by intermolecular hydrogen bonds and stacking interactions. The first key step in the lead compound discovery is identification and validation of target [22]. Numerous technologies have been developed for recognition of targets e.g. bioinformatics tools. In current study, we developed a computational method for identification of target, i.e., exploring the potential binding protein candidates of active natural compounds. This study can be used as a complementary technique in chemical biology and genomics in recognition of targets for other systems. The major limitation of docking is that is that the protein entries are not enough to cover all the protein information of disease-related genomes [28]. However current work depicts additional therapeutic potential of sesquiterpenoids, having capacity to enter into clinical trials. This study along with additional techniques could benefit scientific community for drug designing.

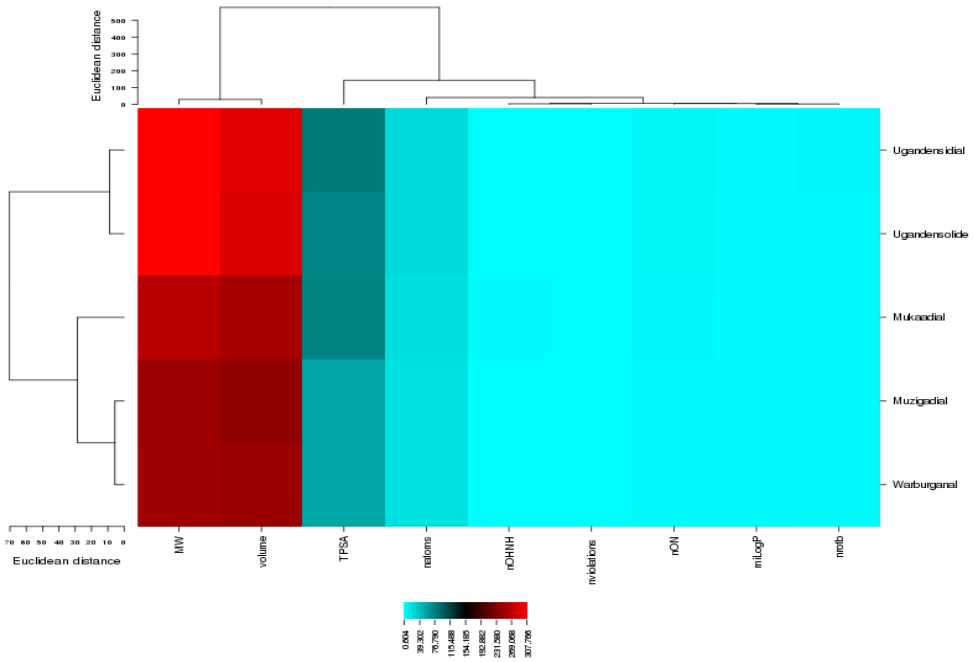

Fig. 2. Heat map indicating the pharmacokinetics (drug likeness properties) and toxicity analysis of sesquiterpenoids derivatives

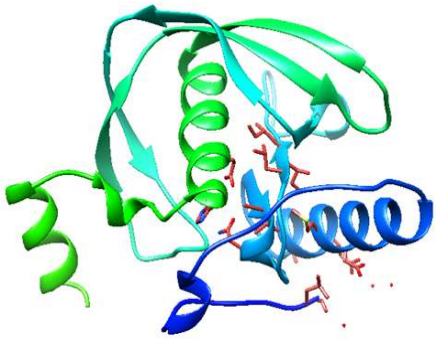

Fig. 3. Crystallographic tertiary structure of *Helicobacter pylori* peptide deformylase

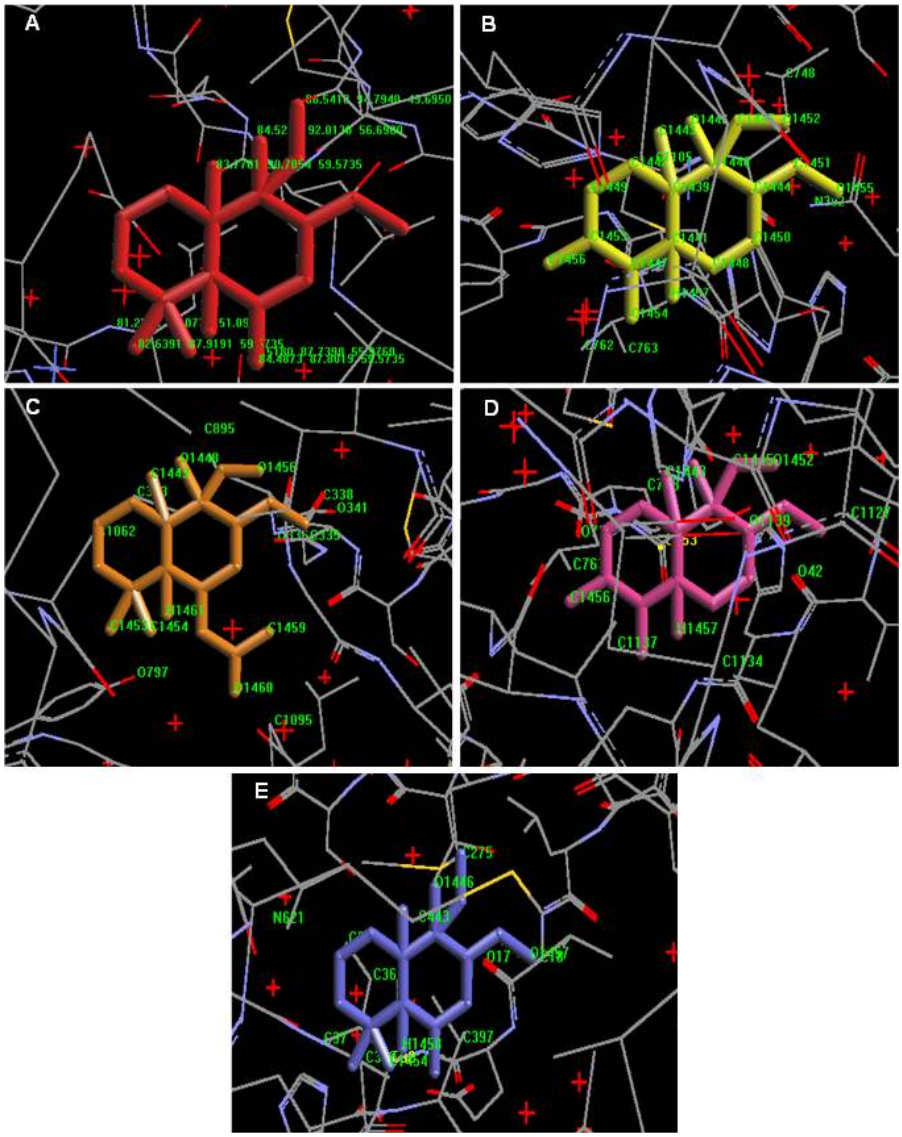

Fig. 4. Docking interaction of peptide deformylase and sesquiterpenoids derivatives (A) Mukaadial (B) Muzigadial (C) Ugandensidial (D) Ugandensolide (E) Warburganal

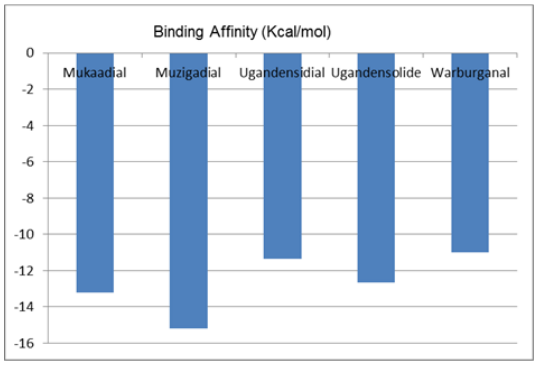

Fig. 5. Energy values obtained during docking analysis of sesquiterpenoids derivatives as ligand molecules and peptide deformylase target protein

4. CONCLUSIONS

In conclusion, molecular docking studies of five sesquiterpenoids showed that these natural compounds are potential ligands to inhibit the peptide deformylase activity and this study could pave the ways in discovery of new lead compounds and molecular targets as potential anti-*H. pylori*.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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