ARTICLE IN PRESS

Saudi Pharmaceutical Journal xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Inverse docking based screening and identification of protein targets for Cassiarin alkaloids against *Plasmodium falciparum*

Arvind Negi [a,1,*], Nitisha Bhandari [b,1], Bharti Rajesh Kumar Shyamlal [c], Sandeep Chaudhary [c,*]

[a] School of Chemistry, National University of Ireland, University Road, Galway H91 TK33, Ireland
[b] School of Biotechnology, Graphic Era University, Dehradun, Bell Road, Society Area, Clement Town, Dehradun, Uttarakhand 248002, India
[c] Laboratory of Organic and Medicinal Chemistry, Department of Chemistry, National Institute of Technology Jaipur, Jawaharlal Nehru Marg, Jaipur 302017, India

ARTICLE INFO

Article history:
Received 6 December 2017
Accepted 31 January 2018
Available online xxxx

Keywords:
Plasmodium falciparum
Inverse docking
Cassiarin alkaloids
Proteomics

ABSTRACT

Various reports have shown Cassiarin alkaloids, selective *in vitro* activities against various strains of *Plasmodium falciparum* with low cytotoxicity, which indicates their possible candidature as antimalarial drug. However, poor recognition of their protein targets and molecular binding behaviour, certainly limits their exploration as antimalarial drug candidature. To address this, we utilises inverse screening, based on three different docking methodologies in order to find their most putative protein targets. In our study, we screened 1047 protein structures from protein data bank, which belongs to 147 different proteins. Our investigation identified 16 protein targets for Cassiarins. In few cases of identified protein targets, the binding site was poorly studied, which encouraged us to perform comparative sequence and structural studies with their homologous proteins, like as in case of Kelch motif associated protein, Armadillo repeats only protein and Methionine aminopeptidase 1b. In our study, we also found Tryptophanyl-tRNA synthetase and 1-Deoxy-D-Xylose-5-phosphate reductoisomerase proteins are the most common targets for Cassiarins.
© 2018 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Malaria is a mosquito-borne infectious disease affecting humans and other animals caused by the protozoan parasite, *Plasmodium*. According to WHO 2015 statistics, 212 million clinical episodes and 429,000 deaths were reported worldwide (Bhatt et al. (2015); World_Health_Organization, 2015; Kamholz, 2016; World_Health_Organization, 2016) and nearly 3.2 billion people are at the risk of malaria, especially children under age of 5 years, pregnant women, immune compromised patients, as well as non-immune migrants (Schumacher and Spinelli, 2012; Negi, 2013; Wells et al., 2015). These large numbers are mainly subjected by *Plasmodium falciparum* (*P. falciparum*), followed by *P. vivax*, *P. ovale*, *P. malariae*, and to some extent *P. knowlesi*. Although in recent years, some profound development has been seen in antimalarial drug discovery, but higher number of resistance cases, mild to moderate selectivity/toxicity ratio of most of the antimalarial drugs, show a need of new scaffolds or new chemical entity (NCE) (Bushell et al., 2017). Moreover, the alkaloid natural product class has been found promising and useful in numerous disease states, as mentioned in these reports (Kayser et al., 2003; Frederich et al., 2008; Özçelik et al., 2011; Singla et al., 2013; Singla et al., 2014). Additionally, alkaloids, such as Quinine, Cryptolepine, Thiaplakortones A–D and their semi or synthetic derivatives (Caniato and Puricelli, 2003; Oliveira et al., 2009) are well studied as antimalarial agents (Cimanga et al., 1997; Davis et al., 2013), showing alkaloidal scaffold inheritance of antiplasmodial activity.

In recent years, various medicinal active natural compounds were reported from a plant, *Cassia siamea* (Leguminosae). Most of these natural compounds are either isolated from leaves (Cassiarin-A, B, G, H, J, K, 5-acetonyl-7-hydroxy-2-methylchromene, Chrobisiamone A) (Morita et al., 2007; Oshimi et al., 2008; Deguchi et al., 2012), or flower (Cassiarin C, D, E, F; 10,11-dihydroanhydrobarakol, anhydrobarakol Cassibiphenol A and Cassibiphenol B) (Thongsaard et al., 2001) (Deguchi et al., 2014),

* Corresponding authors.
E-mail addresses: arvindnegi2301@gmail.com (A. Negi), schaudhary.chy@mnit.ac.in (S. Chaudhary).
[1] Both authors have equal contribution.

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2018.01.017
1319-0164/© 2018 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

or also from twigs (Siamalkaloids A, B, C) (Wu et al., 2016), structures shown in Fig. 1. Surprisingly, Cassiarin-A and Cassiarin-B were found highly selective than Chloroquine against chloroquine sensitive *P. falciparum* 3D7 strain over human breast cancer cell lines (MCF7), as selectivity/cytotoxicity ratio are fairly high, $\geq$4348, $\geq$1112, 3281 for Cassiarin-A, B and Chloroquine, respectively (Morita et al., 2009). Furthermore, their antimalarial role was purposed though their vasorelaxation activity, as prompted by nitric oxide production from the endothelium, which might inhibit the host cell surface attachment of the parasite (Morita et al., 2009). In 2009, Oshimi et al. isolated Cassiarins C-E and 10,11-dihydroanhydrobarakol which showed reasonable *in vitro* selectivity against *P. falciparum* 3D7 over human leukaemia cells (HL-60 cell lines) (Oshimi et al., 2009).

1.1. Chemistry

Isoquinoline is the basic alkaloidal core of Cassiarins, which fused with 2-methyl-2*H*-pyran ring at position [4, 8a], forms tricyclic ring and as prototype represented in the structure Cassiarin-C (shown in Fig. 1). Further derivatization at C_2 position of Cassiarin-C, forms Cassiarin D, E and F. The methyl at C_2 in the pyran ring of these isoforms (Cassiarin-C, D and E), can adopt 2 conformations as *R* or *S*. Every isoform has its own structure signature at C_2 position, when compare to Cassiarin-C structure, which has simply a methyl group: (a) Cassiarin-D has $-CH_2-$ tethered 5-propenone-7-hydroxy-4*H*-chromen-4-one functionality at C_2 with regards to Cassiarin-C, as shown in Fig. 1; (c) Cassiarin E is *Bis*-isomer of Cassiarin-C; (d) Cassiarin-F has fused with a toluene ring, to form a tetracyclic ring at position [2,3] of Cassiarin-C and also has further substructure extension in a form of 2-resorcinol propanone functionality, shown in Fig. 1.

In order, to characterize the molecular targets for these Cassiarin alkaloids, we used inverse docking, which is grown as a valuable tool in drug target identification in recent years. Also, helpful in rediscovering the molecular mechanism of polypharmacological active compounds, especially, the natural products and detecting, the possible adverse side targets of existing drugs as in toxicological studies. Previous reports on inverse docking shows implementation of various methodologies, to improve the accuracy and prioritizing the identified targets. Kumar et al. tried to address the limitations of docking scoring schemes with respect to attain confidence in theoretical binding affinities (Kumar et al., 2014). They presented a reverse approach, where they used the pharmacophore features of the ligand as interactions of complementary amino acids of protein cavities (also, called them as "pseudoreceptor"). These pseudoreceptors were then matched with the cavities/ binding sites of the selected protein dataset. They applied this approach on 3 co-crystallized ligands over 28 proteins of Zea mays and provide an application of the total probability and docking energy, in order to acquire confidence in prioritizing the probable protein targets (Kumar et al., 2014). Also, Carvalho et al. adopted a reverse screening strategy based on ligand similarity and target structure, which resulted into, a number of putative protein target candidates for quercetin polypharmacological effects and also successfully correlated them, with previously tested proteins, mainly protein kinases and poly [ADP-ribose] polymerases (Carvalho et al., 2017). In another report, Kumar et al. compared the rank list results from inverse docking and ligand-based similarity search, assist them to prioritize the chitinase as most probable target for kinetin molecule, further supported by experimental data (Kumar et al., 2015). While, few compiled literature reviews on inverse screening and its application are available, related to the drug repositioning (Kharkar et al., 2014) and available target databases/servers (Lee et al., 2016).

However, the selectivity/cytotoxicity profile of these reported Cassiarin alkaloids has been promising in *P. falciparum* but as their protein targets are poorly recognised, which certainly limits their further exploration as antimalarial candidature. To identify their protein targets and acquire significant confidence in prioritising the identified target, we used reverse screening on all available protein targets from protein data bank, using three different placement docking methods.

2. Materials & methods

2.1. Proteins set

All the protein targets for *P. falciparum* were searched on protein data bank, claiming 1047 structures. After filtering off the NMR and low resolved cryo-electron structures from X-ray structures, proteins were selected and arranged in the order of their crystal structure resolution as an individual target, see in Table 2. In most cases, preferences were given to co-crystallised ligand containing protein structures, otherwise the structures without co-crystallised ligand protein were also selected. Later, the self-docking on co-crystallise ligand containing protein targets, was performed to calculate the minimum RMSD values (min. RMSD values) in order, to evaluate the competency of a particular protein in accommodating of its own co-crystallise ligand (also, called ligandability) (Kumar, 2018). In those structures, which lack co-crystallise ligand, active site finder tool of MOE (Del Carpio et al., 1993; Negi et al., 2013a) was used to find the active surface patches which were saved as dummy atoms for performing the later docking. Also, in certain cases we aligned the target protein sequences with their homologous proteins of other species. These studies involved superposition of three-dimensional structure of the proteins of interest, as to see the overlapped domains and regions with comparative homologous proteins, which could be inferred into key active site residues in those proteins which were poorly studied in the past.

2.2. Ligand set

As absolute stereochemistry at C_2 position of Cassiarins is unknown, therefore we build both (*R*) and (*S*) stereoisomers, which were further minimised by MMFF94x Forcefield. Although, the energy minimisation step showed a reasonable energy difference between both the stereoisomer forms of individual Cassiarins (C, D, E & DBH), but these were used as such in our molecular modelling studies, as to avoid any pseudo positive or misleading results.

2.3. Molecular modelling

The proteins were prepared by, (a) removing of the water molecules from their crystal structures; (b) modelling the missing or breaks in their loops; and (c) protonation of the structure. Later, the co-crystallise ligand binding site or saved dummy atoms on proteins were used for docking of the Cassiarins. This inverse screening was performed by utilising 2 docking placement methods (also called, "Differential placement method based docking"). The first was the alpha triangle placement method, which generates the ligand-protein poses based on the overlapping of ligand atom triplets onto the triplets of protein point sites (are, also called alpha sphere centres). At each iteration cycle, a pose was determine based on sampling of a random triplet of ligand atoms over a random triplet of alpha sphere centres. The following setting was used for this method: minimum and maximum iterations cycles were set 800,000 and 5,000,000 respectively with timeout

Please cite this article in press as: Negi, A., et al. Inverse docking based screening and identification of protein targets for Cassiarin alkaloids against *Plasmodium falciparum*. Saudi Pharmaceutical Journal (2018), https://doi.org/10.1016/j.jsps.2018.01.017

Download English Version:

https://daneshyari.com/en/article/8522347

Download Persian Version:

https://daneshyari.com/article/8522347

Daneshyari.com