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In-Silico Screening Of Certain Bioactive Compounds From *Ceasalpania bonduc* (Fever Nut) For Select Class I And II Type Human Olfactory Receptors (ORs) Against Asthma And COPD.

B Nagarathnam[1], A Gandhimathi[2], J Philip Robinson[3], P Ponmurugan[4], V Balakrishnan[5], and R Sowdhamini[6]*.

[1,2,6]National Center for Biological Sciences (TIFR), Bangalore, India.
[3]Department of Biotechnology, K.S. Rangasamy College of Technology, Tiruchengode, Namakkal Dt, Tamil Nadu, India.
[4]Department of Botany, Bharathiar University, Coimbatore, Tamil Nadu, India.
[5]PG and Research Department of Botany, Arignar Anna Govt. Arts College, Namakkal, Tamil Nadu, India.

ABSTRACT

Olfactory receptors (OR) belong to trans membrane proteins (GPCRs) and are effective drug targets. The occurrence of class I (sense water-borne odors) and class II type (sense air-borne odors) human ORs not only depict odor diversity, but also illustrates receptor specificity. Insilico screening showed significant docking scores for the compounds from *Ceasalpania bonduc* (Kantkarej in Hindi, Kuberakshi in Sanskrit) and are close to the commercial drug theophylline, other familiar natural compounds. Further, these findings suggest the pharmacological features, novel compounds of the herb to treat asthma, chronic obstructive pulmonary disease (COPD), malaria and can be used in aromatherapy, intra nasal drug delivery (INDD) -a painless drug delivery system.

Keywords: *In-Silico, Ceasalpania bonduc,* human olfactory receptors, COPD.

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Corresponding author

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INTRODUCTION

Screening of bioactive compounds from medicinal herbs, play an important role in finding potential novel compounds for therapeutic use. Plants with vast array of secondary metabolites, form a reservoir of low molecular weight, organic compounds that is largely untapped, as a source of pharmaceuticals. Although hundreds of plant species have been tested for pharmacological properties, majority of compounds have not been adequately evaluated. Thus the current study is aimed to identify the binding affinity of bioactive compounds from *Ceasalpania bonduc*, familiar natural compounds from other plants (cinchona, eucalyptus, ocimum) and a commercial drug theophylline with selected class I and class II type human olfactory receptors to treat asthma and COPD.

As per World Health Organization (WHO), more than 90% of COPD related deaths occur in developing countries. And alarmingly, Global Burden of Disease study 2017 state that asthma continues to be the 12th leading cause of deaths across all ages in India since 1990. Hence exploring and applying traditional medicinal practices, effective use of plant metabolites for aromatherapy and intra nasal drug delivery are the need of the hour. The outcome of insilico screening would be helpful to understand the feasibility of screened novel compounds further to evaluate through invitro and invivo analysis and to design novel drugs.

Medicinal Properties of *Ceasalpania bonduc*

Ayurvedic pharmacology describes the attributes of *Ceasalpania bonduc* in a different system of traditional medication, for the treatment of diseases, ailments. And various ayurvedic textual indications, refer not only about the nutraceutical potentials but also for several medicinal properties such as anti-asthmatic, anti- diabetic, anti-inflammatory, anti-oxidant, anti-bacterial, anti-filarial, anti-tumor, anxiolytic, immunomodulatory, hypoglycemic activity (Kakade et al 2017).

The prevalence of the chemical groups such as alkaloids, glycosides, terpenoids and saponins of the herb is useful in phytomedicine (Vigasini Subbiah et al 2019) . Recent studies clearly show that 70% ethanolic extract of seeds of the plant *Caesalpinia bonducella* is effective in the prophylaxis management of asthma (Khandagale et al 2019).

METHODS

Collection of bioactive compounds

Based on lipinski rule of five, properties such as molecular mass, lipophilicity, hydrogen bond donors, hydrogen bond acceptors of the bio active compounds -bonducellin, caesaldekarin-C, caesaldekarin-F, caesalpinin, carebastine, E-caesalpin, F-caesalpin of *Ceasalpania bonduc*, other familiar natural compounds such as kaempferol (natural flavonol), cirsimaritin (cinchona alkaloids), eucalyptol (cyclic ether, monoterpenoid from eucalyptus), eugenol (phenylpropanoid from ocimum) and a commercial drug (theophylline) were considered for the study.

Collection of Olfactory receptors

Our earlier publications on DOR - Data base of olfactory receptors (B.Nagarathnam et al 2014), phylogenetic subclustering of human olfactory receptors helped to select representative ORs from class I and II type (B.Nagarathnam, 2017). Representative ORs from class I type (sense water-borne odors) such as 1_HS51E2, 1_HS52A4, 1_HS52N5, 1_HS56A1, 1_HShCG28336 and representatives ORs from class II type (sense air-borne odors) such as 2_HS1M1, 2_HS10A2, 3_HS10G2, 4_HS5M8, 6_HS5AN1, 8_HS10J1, 8_HS10H1, 9_HS13D1, 10_HS2T4, 10_HS2T3 has been used for the current docking studies.

Among the ten OR clusters, cluster one belongs to class I type, and cluster two to ten are of class II type and each cluster is denoted with a prefix of cluster number along with _HS for homo sapiens. Example : 1_HS51E2 is from cluster 1 of class I type , 2_HS1M1 is from cluster 2 of class II type.

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Virtual screening

The secondary structure of selected ORs were predicted using **Pyre 2** server and validated using Ramachandran plot. Docking (XP docking) was performed using **GLIDE** (Grid-based ligand docking with Energetics) of schrodinger suite (Harini K, Sowdhamini R. 2015). The MD simulations were carried out using desmond module of the GLIDE software for 20 ns using the OPLS_2005 force field without solvent. And the obtained Glide score (G-score), ligand-interaction diagram was helpful to identify the significant binding partners (refer **figure** 1).

Figure 1: Methodology for insilico screening of photoconstituents

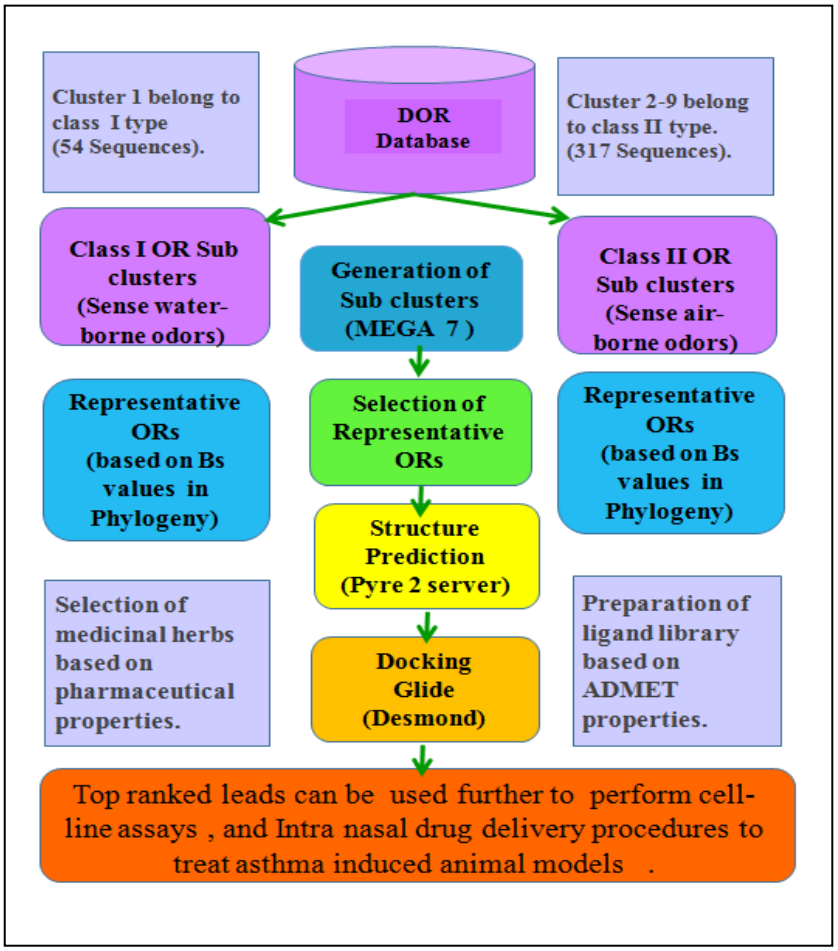

Figure 1: Step -wise procedure for selection of sequences, prediction of secondary structure, and docking has been illustrated with respective tools and parameters to propose best binding compounds with ORs.

RESULT AND DISCUSSION

Binding affinity with class I type receptors

Among the selected bioactive compounds, bonducellin of *Ceasalpania bonduc* showed significant binding score similar to the commercial drug theophylline and other familiar compounds in use (refer **Table 1**). And It binds to class I type receptors (sense water soluble odour) with the G score ranging from -2 to -8. Bonducellin binds with the receptor 1_HS52A4 with more significant G score (refer **Figure 2**), whereas it was not binding with the 1_HS52N5 receptor, which clearly illustrates the receptor specificity of the compound bonducellin.

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Notably, among the selected receptors, 1_HS52A4 is the only receptor that binds significantly with almost all the bioactive compounds of *Ceasalpania bonduc,* familiar natural compounds and commercial drug. This shows the broader spectrum of chemical perception of this particular class I type receptor.

In contrast, none of the compounds have showed binding affinity with the receptor 1_HS52N5, which clearly demonstrates the binding preference of compounds or limited functionality of this particular receptor. Compounds caesalpinin, E-caesalpin do not bind to any of the given human class I type receptors, can be due to the feature of moderately soluble as predicted from Swiss ADME, wherein E-caesalpin is much popular for its antimalarial activity.

Peculiarly, the receptor 1_HS52N5 prefers to bind only with a commercial drug theophylline with the significant G-score, which does not bind to the natural compounds, that needs to be explored further with nearest homologs (mouse, rats ORs) for the prediction of evolutionary trends in sensing chemically synthesized compounds in great detail.

Figure 2: Interaction of bonducellin with class I type olfactory receptor 1_HS52A4

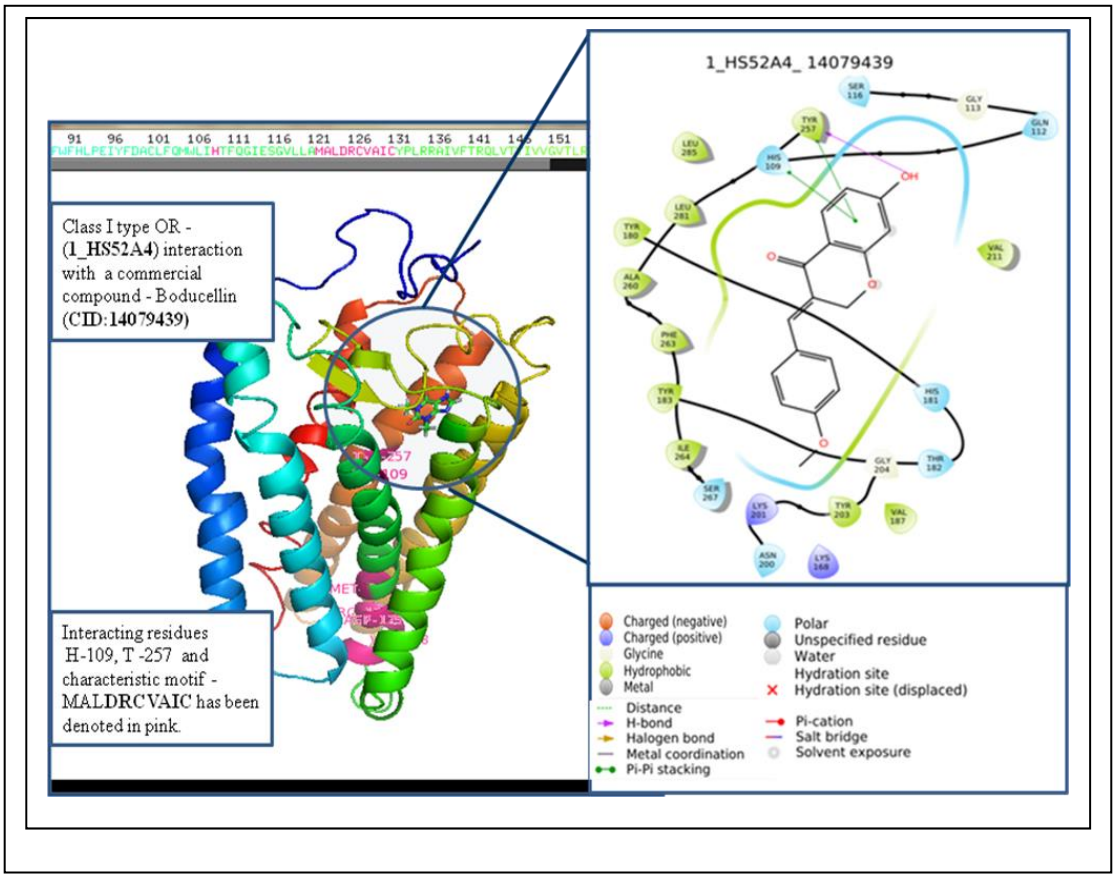

Figure 2: Case study of human class I type olfactory receptor binding to bonducellin compound from ***Ceasalpania bonduc*** depicts the broader spectrum of affinity with class I type ORs. In the given illustration, H -109 ,Y-257 residues of 1_HS5A4 receptor showwed interaction (Pi-Pi stacking, H-bond) with the compound bonducellin. And the distance of H-A is 2.81 , D-A is 3.47, donor angle is 122.86 for His-109 ; the distance of H-A is 2.20, D-A is 3.09, donor angle is 157.61 for TYR-257 detected by PLIP-Protein-ligand interaction profiler.

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Table 2: Binding scores with class I type ORs

S.No	Compound (Pubchem ID)	1_HS51E2	1_HS52A4	1_HS52N5	1_HS56A1	HShCG28336
1	Bonducellin (14079439)	-2.47	-8.178		-5.57	-6.377
2	Caesaldekarin C (10712612)		-8.425			
3	Caesaldekarin F (15381600)		-8.431			
4	Caesalpinin (15329770)					
5	Carebastine (65820)		-8.386			
6	E-Caesalpin (11282647)					
7	F-Caesalpin (15381600)		-7.653			
8	Theophylline (2153)	-5.979	-4.103	-2.29	-4.64	-6.233
9	Kaempferol (5280863)	-8.647	-8.742		-6.6	-7.495
10	Cirsimaritin (188323)	-6.899	-8.739			-6.861
11	Eucalyptol (2758)	-3.694	-5.374		-4.46	-3.689
12	Eugenol (3314)	-5.676	-6.3	-4.82	-6.15	-5.301

Binding affinity with class II type receptors

The screening of binding affinity of bonducellin showed significant results with the class II type (sense air -borne odor) olfactory receptors also. This again proves bonducellin as the key component in the herb (Purshothaman KK et al 1982) for its functional influence in the immunomodulatory activity (Al-Snafi, et al 2015).

The compound Caesalpinin showed very significant G score (-9. 637), carebastine exhibited the most significant G-score (-7.938) with the receptor 8_HS1OJ1 ,) (refer **Table 2**). This depicts the functional influence, preference to the human class II type receptor.

Interestingly, the compound F-caesalpin (Komal Moon et al 2010) binds only to the cluster 8 . Among all the clusters, cluster 3, 8, and 10 showed favorable binding affinity with the selected compounds, which proves receptor specificity at cluster level (i.e., OR cluster specificity).

The compound caesaldekarin C binds favorably with cluster 2,3,6,8 of class II type receptors, wherein ORs of cluster 4 does not bind with any of the compounds from *Ceasalpania bonduc*, but they significantly bind with the commercial drug and other familiar natural compounds (A case study is given in **figure 3** from cluster 4). This clearly demands the scope of studying the chemo perception of olfactory receptors based on ligand chemistry. Also, this pilot study can be further compared with the endogenous ligand of mouse ORs (Eugenol) (Harini et al 2015) for the detailed study on interacting residues for the promiscuous receptors HS52A4 from class 1 type 3_HSI0G2 , 8_HS1OJI and 10_HS2T4 of class II type.

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Figure 3: Interaction of commercial drug with class II type olfactory receptor 4_HS5M8

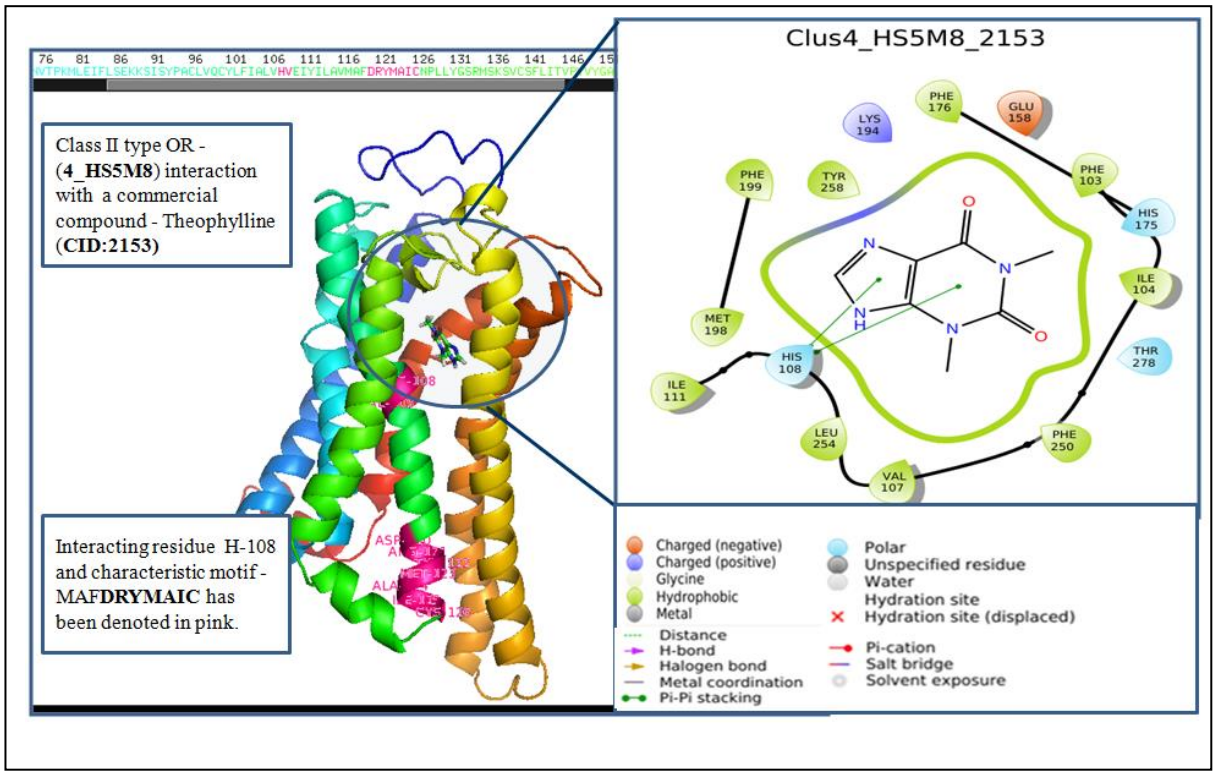

Figure 3: Case study of human class II type olfactory receptors binding to commercial drug - theophylline emphasizes the receptor specificity. In the given illustration, H -108 residue of 4_HS5M8 receptor showed interaction (Pi-Pi stacking) with the compound theophylline. And the distance of H-A is 2.13 , D-A is 3.13, donor angle is 170.58 detected by PLIP-Protein-ligand interaction profiler.

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Table 2 : Binding scores with class II type ORs

S.no	Compound (Pubchem ID)	2_HS1M1	2_HS10A2	3_HS10G2	4_HS5M8	6_HS5AN1	8_HS10J1	8_HS10H1	9_HS13D1	10_HS2T4	10_HS2T3
1	Bonducellin (14079439)	-6.751	-8.184	-7.065		-6.884	-8.134	-9.421	-6.211	-5.199	
2	Caesaldekarin C (10712612)		-6.252	-8.827		-8.913	-8.258			-3.432	
3	Caesaldekarin F (15381600)		-6.392	-8.642		-7.826	-7.985			-4.039	
4	Caesalpinin (15329770)					-7.074	-9.637				
5	Carebastine (65820)			-5.776		-6.383	-7.938			-2.77	
6	E-Caesalpin (11282647)						-9.9				
7	F-Caesalpin (15381600)						-8.988				
8	Theophylline (2153)	-4.582	-6.562	-5.385	-6.58	-4.422	-5.468	-4.309	-6.149	-4.685	-4.808
9	Kaempferol (5280863)	-7.701	-6.655	-7.947	-8.654	-9.436	-8.886	-7.381	-7.852	-5.813	-8.24
10	Cirsimaritin (188323)	-7.069	-7.024	-4.441	-8.502	-6.657	-8.37	-9.718	-7.18	-6.001	
11	Eucalyptol (2758)	-4.469	-5.304	-6.137	-7.178	-5.372	-5.762		-4.964		
12	Eugenol (3314)	-5.095	-5.949	-6.556	-6.785	-6.846	-5.728	-7.153	-5.373	-5.862	-7.154

CONCLUSION

In essence, the current study illustrates the importance of screening the bioactive compounds of *Ceasalpania bonduc* to understand the ligand and receptor specificity with regards to class I and II type receptors in detail. This in turn pave way to utilize purified compounds in aromatherapy to treat diseases such as asthma, COPD, malaria using invitro assays such as cytotoxicity , assesment of anti-inflammation, and invivo studies to evaluate the effect of mentioned compounds to treat asthma induced animal models , finally to recommend novel drugs through green chemistry.

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