Pharmacogn J. 2018; 10(4):814-817
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com | www.journalonweb.com/pj | www.phcog.net

Original Article

Immunoinformatics Study of Procyanidins as Mast Cell Stabilizers

Anamika Basu[1*], Anasua Sarkar[2], Piyali Basak[3]

ABSTRACT

Background: Allergens are foreign proteins that stimulate the production of immunoglobulin E (IgE), when they come in contact with human body. These allergens after binding with IgE through FcεRI receptor, triggers the signal transduction reaction in mast cell and basophil cells, leading to allergic reactions by releasing some mediators. Four correctly written as surface-exposed tryptpphans Trp 87, Trp 110, Trp 113 and Trp 156 of FcεRI receptor protein,play significant role in IgE and FcεRI receptor binding interaction. Polyphenols in apple are proven effective for allergic rhinitis treatment by preventing degranulation of granulocytes. **Objective**:To prevent release of mediators like histamine etc., a therapeutic strategy can be designed by inhibiting IgE and FcεRI receptor interactions.This strategy may provide a symptomatic treatment for allergic reactions due to exposure to pollen allergens. **Materials and methods:** Molecular docking studies are used to analyse the IgE with FcεRI receptor binding in presence and absence of procyanidin molecules, present in apple. **Results:** For procyanidin molecules, binding affinity of IgE molecule with its high affinity receptor (FcεRI receptor)decreases markedly. Thepositions of Trp 87, Trp 110, Trp 113 and Trp 156 are changed for the presence of procyanidin C1 molecule. Since IgE and FcεRI receptor binding is highly affected in presence of procyanidin C1, so this compound can inhibit mast cell degranulation by altering the binding affinity of IgE with its its high affinity receptor (FcεRI receptor). **Conclusion:** Procyanidin C1 can be used as natural anti-allergic drug by stabilizing mast cells during pollen allergic reaction after experimental verification.

Keywords: Allergy, IgE, IgE receptor FcεRI, Mast cell stabilizer, Molecular docking, Procyanidins, Tryptophan residues.

Anamika Basu[1*], Anasua Sarkar[2], Piyali Basak[3]

[1]Lecturer, Department of Biochemistry, Gurudas College, Kolkata, West Bengal, INDIA.
[2]Assistant Professor, Computer Science and Engineering Department, Jadavpur University,Kolkata, West Bengal, INDIA.
[3]Director,School of Bioscience and Engineering, Jadavpur University, Kolkata, West Bengal, INDIA.

Correspondence

Mrs. Anamika Basu

Lecturer, Department of Biochemistry, Gurudas College,Kolkata, West Bengal, INDIA.

Phone no : 9830279500

E-mail: basuanamikaami@gmail.com

History
- Submission Date: 26-02-2018;
- Revised Date: 14-03-2018;
- Accepted Date: 19-04-2018

DOI : 10.5530/pj.2018.4.138

Article Available online
http://www.phcogj.com/v10/i4

INTRODUCTION

Pollen allergens when come to contact human body e.g. skin, respiratory tract, react with antibodies (immunoglobulin type E or IgE) and produce allergic reactions, also known as immediate-type hypersensitivity reactions. Allergen bound IgE, which is synthesized in response to allergens during allergic reaction, becomes fixed to specific receptor on the membranes of mast cells and basophils. The high-affinity IgE receptor FcεRI on mast cells and basophils, is a heteromeric protein containing αßγ2 subunits. Binding of IgE to FcεRI occurs through direct interactions between Cε3 domains of the heavy chains (Fc) of IgE and the extracellular domains of FcεRIα. α subunit of FcεRI receptor binds with IgE molecules with high affinity through four surface exposedtryptophan's (W110, W113, W156 and W87).[1,2] This binding plays significant role in initiating intracellular signaling cascades inside mast cell and controls secretion of allergic mediators e.g. histamine.[3] A large conformational rearrangement occurs in IgE structure during its binding with high affinity receptor.[4,5] A novel strategy for antiallergic treatment can be postulated by designing molecules that can affect the receptor binding affinity of IgE.[6,7]

Mast cell stabilizer block mast cell degranulation, stabilizing the cell and thereby preventing the release of histamine[8] and related mediators e.g. leukotrienes (for basophils) and prostaglandin D2 and IL-5 (for mast cells) during hypersensitivity reaction. Though innumerable synthetic mast cell stabilizers are present[9] in our medicinal science, but the search for suitable natural product as mast cell stabilizer is still going on.[10] Comparative study shows that higher efficiency for natural product quercetin than synthetic compound cromolyn for inhibiting allergic reactions.[11] Several inhibitors of IgE:FcεRI binding have been identified e.g. an anti-IgE therapeutic antibody (omalizumab) , an engineered protein inhibitor, DARPin E2_799–11, which are used to treat severe allergic asthma.[12,13]Polyphenols which are abundant in apple are proven effective for allergic rhinitis treatment by preventing degranulation of granulocytes in mast cells.[14,15,16] Procyanidins are polymeric form of catechins. In apple, almost 50% to 60% polyphenols are oligomers and polymers of catechins.Dimeric catechins are procyanidin B1, B2, C1 present in apple extract shows antiallergic activity on rhinitis treatment. Among them, procyanidin C1 extracted from unripe apples (*Rosaceae mal-*

Cite this article: Basu A, Sarkar A, Basak P. Immunoinformatics Study of Procyanidins as Mast Cell Stabilizers. Pharmacog J. 2018;10(4):814-7.

lus) shows anti-allergic effect by various mechanisms e.g. FcεRI induced degranulation and cytokine production of mast cells. Procyanidin C1 which is related with intra- cellular signalling pathway,prevents FcεRI-mediated mast cell activation.[17] The flow cytometric study is confirmed that polymeric procyanidins supress the binding of IgE antibody to FcεRI.[17] But the molecular mechanism for inhibitory effect on antibody IgE with FcεRI binding is unknown to all. A compound must have an anti-allergic activity if it inhibits the binding between Ig E antibody and FcεRI receptor during type I hypersensitivity reaction.

Comparative studies on different procyanidins structures and physico-chemical properties using computational methods will help us to identify apple extract, as herbal medicine in allergic reactions. Computational docking studies are used to elaborate the mechanism of action of various natural products e.g. quercetin glycosides as inhibitor of angiotensin-converting enzyme for the treatment of myocardial infarction[18]and fatty acids of black cumin oil as inhibitors of P-glycoprotein to improve pharmaceutics of many lifesaving drugs.[19]

MATERIALS AND METHODS

X-ray crystallographic structures for human IgE, FcεRIreceptor

The three-dimensional structure of IgE (PDBID 4J4P) and FcεRI receptor (PDBID 1F2Q) are downloaded from the RCSB protein Data Bank.[20]

2D and 3D structures of procyanidin B1, B2, C1 and C2

The chemical structures of four procyanidin molecules B1, B2, C1 and C2 are obtained from ZINC database.[21] MOL SDF format of these ligands are converted to mol2 file using UCSF Chimera tool.[22]

Molecular docking study

Molecular docking is a computational method, which forecasts the preferred positioning of two protein molecules e.g.IgE and FcεRI receptor when bound to each other and form a stable complex using ClusPro 2.2 server.[23] Docking study is also used here to investigate the binding affinity of IgE and FcεRI receptor in presence of four small molecules e.g. procyanidin B1, B2, C1, C2 using SwissDock.[24] Binding efficiency of four procyanidin molecules with FcεRI receptorin absence of IgE molecule with the help of both SwissDock[24] and ClusPro 2.2[23] server is estimated. With the help of lowest binding energy,the procyanidin molecule which act as best mast cell stabilizer, can be identified using the formula-E = 0.40E_{rep} + -0.40E_{att} + 600E_{elec} + 1.00E_{DARS}. Here, repulsive, attractive, electrostatic as well as interactions extracted from the decoys as the reference state, are considered for structure-based pairwise potential calculation in docking.[25] Visualization of docking structures with USCF Chimera,[22] helps to calculate the distances and torsional angle distortion of binding, with IgE and FcεRI receptor in presence of four procyanidin molecules. The positions of four surface – exposed tryptophan's (W110, W113, W156 and W87) molecules which are responsible for α subunit of FcεRI receptor binding with IgE molecules with high affinity, are distorted due to presence of procyanidin molecule. This distortion affects the binding affinity of IgE molecule with its high affinity receptor.

RESULTS

Docking result

α subunit of FcεRI receptor binds with IgE molecules (Figure 1) with high affinity through four surface – exposed tryptophan's (W110, W113, W156 and W87) (Figure 2) with lowest binding energy -970.3.

Interactions of procyanidin B1, B2, C1 and C2 with FcεRI receptor

For procyanidin C1, interacting amino acids are Met 98 and Leu 9 of FcεRI receptor, which form H bonds with two oxygen atoms along

Figure 1: Binding ofIgE withFcεRIreceptor.

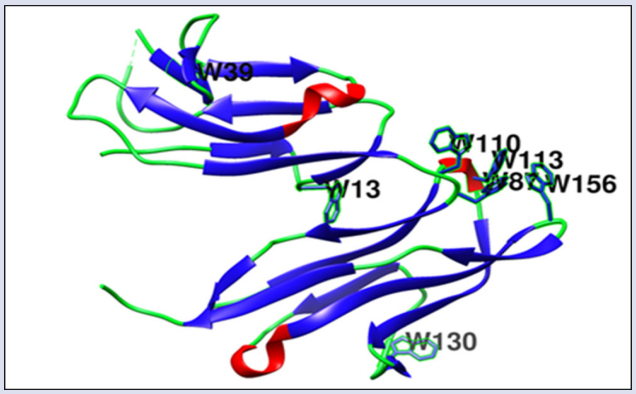


Figure 2: Four surface exposed tryptophan's of FcεRI receptor.

2.033 Å and 2.027 Å bond lengths. Similarly, procyanidin B1 with its O5 atom forms H bond with Met 98 of FcεRI receptor with bond distance 1.855 Å (Figure 3).

Considering binding energy values, it can be concluded that procyanidin C1 molecule stabilises IgE and FcεRI receptor complex, most efficiently than the other three compounds (-9.053922 Kcal/mole) (Table 1). All the four procyanidin molecules B1, B2, C1 and C2, form stable complexes with high affinity receptor FcεRI and their binding energies are shown in Table 2. Binding energy of docking compound IgE and FcεRI receptor is -970.3 where IgE is ligand protein and its receptor is FcεRI protein. When procyanidin C1binds with FcεRI receptor binding energy is -811.4 Kcal/mole.

Binding energy calculation

Binding energies of different docking structure obtained from ClusPro 2.0 and SWISSDock servers are shown in Table 1 and 2. Thesedocking structures are compared to hypothesize the effect of IgE molecule on bound structure of procyanidine B1, B2, C1 and C2 with FcεRI receptor.

Table 1: Binding energy of IgE with its high affinity receptor in presence and absence of procyanidin molecules.

Docking structures	Lowest binding energy
IgE and FcεRI receptor	-970.3 (For ClusPro 2.0)
IgE and FcεRI receptor and procyanidin B1	-8.685186 (For SWISS Dock)
IgE and FcεRI receptor and procyanidin B2	-8.977657 (For SWISS Dock)
IgE and FcεRI receptor and procyanidin C1	-9.053922 (For SWISSDock)
IgE and FcεRI receptor and procyanidin C2	-8.803351 (For SWISSDock)

Table 2: Binding energy of procyanidin molecules with FcεRI receptor.

Name of compounds	Lowest binding energy	
	For SWISSDock ΔG Kcal /mol	For ClusPro 2.0
Procyanidin B1+ FcεRI	-8.715616	-953.3
Procyanidin B2 + FcεRI	-9.348962	-818.4
Procyanidin C1 + FcεRI	-9.112617	-811.4
Procyanidin C2 + FcεRI	-9.834533	-854.3

Table 3: Distance deviation between amino acids TRP 87, TRP 110, TRP156 in two structures.

Procyanidin C1+ FcεRI + IgE (#0)	Procyanidin C1 + FcεRI (#1.1)	Distance
# 0 Trp 87 CH_2	# 1.1 Trp 87 CH_2	2.535 Å
#0 TRP 156 CZ2	#1.1 TRP 156 CZ2	1.160 Å
# 0 TRP 110 NE1	# 1.1 TRP 110 NE1	0.750 Å

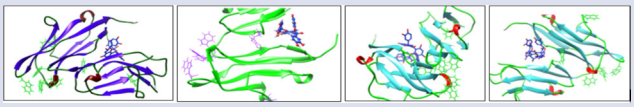


Figure 3: Interactions of procyanidin B1, B2, C1 and C2 with FcεRI receptor.

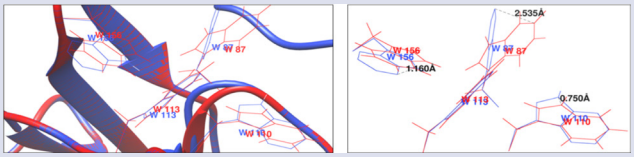


Figure 4: Positional changes in four surface exposed tryptophan molecules in presence and absence of IgE molecule.

Table 4: Torsional angle change.

Procyanidin C1+ FcεRI + IgE (#0)		Procyanidin C1 + FcεRI (#1.1)		Deviation in Torsion angle
ATOM1	ATOM2	ATOM3	ATOM4	
# 0 Trp 87 CE3	# 0 Trp 87 CZ3	# 1.1 Trp 87 CZ3	# 1.1 Trp 87 CE3	-0.482
# 0 TRP 110 NE1	# 0 TRP 110 CE2	# 1.1 TRP 110 NE1	# 1.1 TRP 110 CE2	-178.286
#0 TRP 156 CD2	#0 TRP 156 CE2	#1.1 TRP 156 CD2	#1.1 TRP 156 CE2	-176.830

Conformational change

α subunit of FcεRI receptor binds with IgE molecules with high affinity through four surface – exposed tryptophans (W110, W113, W156 and W87).When allergen comes in contact with human body , the allergen binds through antigen binding sites of IgE molecule. This allergen bound IgE interacts with its high affinity receptor, which is present on mast cell of human body. In presence of procyanidin C1, a major conformational change occurs in α subunit of FcεRI receptor. The distorted structure of receptor protein with Trp 87, Trp 110, Trp 119 and Trp 156, can be visualized in Figure 4.

Binding Procyanidin C1 with FcεRI receptor after binding with IgE (Model no. 0) shown in blue and binding Procyanidin C1 with FcεRI receptor in absence of IgE (Model no. 1.1) shown in red. Positional distortion of four tryptophans W87, W110, W113 and W156 shown in second part.

Conformational change in four tryptophan molecules of *α* subunit of FcεRI receptor, when bound with procyanidin C1, in presence and absence of IgE molecule are calculated by bond distance deviation and deviation in torsional angles in Tables 3 and 4.

DISCUSSION

During type I hypersensitivity reaction, allergen binds with IgE molecule. Allergen bound IgE after binding with high affinity FcεRI receptor, triggers signalling pathway in mast cell. Thus, degranulation reaction starts (release of histamine etc.) from mast cells. Procyanidin molecules which are present in apple in much higher extent, can bind with high affinity receptor of mast cells spontaneously with negative binding energy from molecular docking study. In presence of IgE molecule, which is responsible for mediating allergic reaction, binding energies of procyanidin- FcεRI complex, are transformed. Not only that, four surface exposed tryptophan residues which are responsible for IgE- FcεRI interaction, are distorted in their 3D positions in protein, in absence and presence of IgE. This conformational change in procyanidin- FcεRI complex affects the signal transduction pathway in mast cell degranulation. Thus, procyanidin molecules, specifically procyanidin C1, can inhibit binding of IgE with its high affinity receptor present on biological membrane of mast cell. So, procyanidin molecules can be projected as therapeutic agent (mast cell stabilizers), present in natural resources, in type I hypersensitivity reaction with further experimental verification.

CONCLUSION

This study has shown that procyanidin C1, a polyphenol, present in apple, can be used as natural anti-allergic drug by stabilizing mast cell during type I hypersensitivity reaction after proper experimental verification.

CONFLICT OF INTEREST

There is no conflict of interest

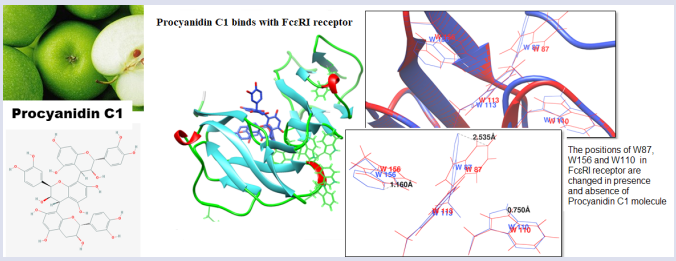
ABBREVIATIONS

IgE- Immunoglobulin E;FcεRI- Fcε receptor I; Trp- Tryptophan amino acid (W);Fc- Fragment of crystallization;Cε3- Constant region of ε heavy chain domain 3; IL 5- Interleukin 5; DARPins- Designed ankyrin repeat proteins;

REFERENCES

1. Garman SC, Kinet JP, Jardetzky TS. Crystal structure of the human high-affinity IgE receptor. Cell. 1998;95(7):951-61.
2. Garman SC, Wurzburg BA, Tarchevskaya SS, Kinet JP, Jardetzky TS. Structure of the Fc fragment of human IgE bound to its high-affinity receptor FcεRIε. Nature. 2000;406(6793):259-66.
3. Turner H, Kinet JP. Signalling through the high-affinity IgE receptor FcεRI. Nature. 1999;402(6760 S):24-30.4.Hulett MD, Brinkworth RI, McKenzie IF, Hogarth PM. Fine structure analysis of interaction of FcεRI with IgE. Journal of Biological Chemistry. 1999;274(19):13345-52.
4. Hulett MD, Brinkworth RI, McKenzie IF, Hogarth PM. Fine structure analysis of interaction of FcεRI with IgE. Journal of Biological Chemistry. 1999 May 7;274(19):13345-52.
5. Stamos J, Eigenbrot C, Nakamura GR, Reynolds ME, Yin J, Lowman HB,*et al.* Convergent recognition of the IgE binding site on the high-affinity IgE receptor. Structure. 2004;12(7):1289-301.
6. Sandomenico A, Monti SM, Palumbo R, Ruvo M. A new FcεRI receptor-mimetic peptide (PepE) that blocks IgE binding to its high affinity receptor and prevents mediator release from RBL 2H3 cells. Journal of Peptide Science. 2011;17(9):604-9.
7. Zhang T, Finn DF, Barlow JW, Walsh JJ. Mast cell stabilisers. European journal of pharmacology. 2016;778:158-68.
8. Baba A, Tachi M, Ejima Y, Endo Y, Toyama H, Matsubara M,*et al.* Anti-allergic drugs tranilast and ketotifen dose-dependently exert mast cell-stabilizing properties. Cellular Physiology and Biochemistry. 2016;38(1):15-27.
9. Finn DF, Walsh JJ. Twenty-first century mast cell stabilizers. British Journal of Pharmacology. 2013;170(1):23-37.
10. Weng Z, Zhang B, Asadi S, Sismanopoulos N, Butcher A, Fu X,*et al.* Quercetin is more effective than cromolyn in blocking human mast cell cytokine release and inhibits contact dermatitis and photosensitivity in humans. PloS One. 2012;7(3):e33805.
11. D'Amato G, Perticone M, Bucchioni E, Salzillo A, D'Amato M, Liccardi G. Treating moderate-to-severe allergic asthma with anti-IgE monoclonal antibody (Omalizumab). An update. Eur Ann Allergy Clin Immunol. 2010;42(4):135-40.
12. Kim B, Eggel A, Tarchevskaya SS, Vogel M, Prinz H, Jardetzky TS. Accelerated disassembly of IgE-receptor complexes by a disruptive macromolecular inhibitor. Nature. 2012;491(7425):613-7.
13. Enomoto T, Nagasako AY, Kanda T, Ikeda M, Dake Y. Clinical effects of apple polyphenols on persistent allergic rhinitis: A randomized double-blind placebo-controlled parallel arm study. Journal of Investigational Allergology and Clinical Immunology. 2006;16(5):283.
14. Kishi K, Saito M, Saito T, Kumemura M, Okamatsu H, Okita M,*et al.* Clinical efficacy of apple polyphenol for treating cedar pollinosis. Bioscience, Biotechnology, and Biochemistry. 2005;69(4):829-32.
15. Tokura T, Nakano N, Ito T, Matsuda H, Nagasako AY, Kanda T,*et al.* Inhibitory effect of polyphenol-enriched apple extracts on mast cell degranulation *in vitro* targeting the binding between IgE and FcεRI. Bioscience, Biotechnology, and Biochemistry. 2005;69(10):1974-7.
16. Nakano N, Nishiyama C, Tokura T, Nagasako AY, Ohtake Y, Okumura K,*et al.* Procyanidin C1 from apple extracts inhibits FcεRI-mediated mast cell activation. International Archives of Allergy and Immunology. 2008;147(3):213-21.
17. Muhammad SA, Fatima N. *In silico* analysis and molecular docking studies of potential angiotensin-converting enzyme inhibitor using quercetin glycosides. Phcog Mag. 2015;S1:123-6.
18. Ali B, Sajid JQ, Mir SR, Shams S, Al-Wabel NA, Kamal MA. *In silico* analysis for predicting fatty acids of black cumin oil as inhibitors of P-glycoprotein. Phcog Mag. 2015;S4:606-10.
19. http://www.rcsb.org/pdb/home/home.do
20. zinc.docking.org/
21. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, *et al.* UCSF Chimera–a visualization system for exploratory research and analysis J Comput Chem. 2004;25(13):1605-12.
22. Kozakov D, Hall DR, Xia B, Porter KA, Padhorny D, Yueh C,*et al.* The ClusPro web server for protein-protein docking. Nature Protocols.2017;12(2):255-78.
23. Grosdidier A, Zoete V, Michielin O. SwissDock, a protein-small molecule docking web service based on EADock DSS. Nucleic Acids Research. 2011;39(S2):W270-7.
24. Kozakov D, Brenke R, Comeau SR, Vajda S. PIPER: An FFT-based protein docking program with pairwise potentials. Proteins: Structure, Function, and Bioinformatics. 2006;65(2):392-406.

GRAPHICAL ABSTRACT



ABOUT AUTHORS

Anamika Basu: Is an Lecturer in Dept. of Biochemistry, Gurudas College in Kolkata. She received her M.Sc. degree in Biochemistry from Kalyani University and M.Tech in Biotechnology from Jadavpur University. She teaches Immunology, Molecular biology, Cell Biology and Clinical Biochemistry in graduate and post-graduate level. She is a co-author of four book chapters and several journal papers and conference papers. Her research interest includes Computational Biology, Bioinformatics, Molecular modeling, Molecular docking, Molecular Biology and Plant Biology.

SUMMARY

The search for natural antiallergic compounds from plants is an innovative idea for new drug development. Several researchers have been identified various phytochemicals as mast cell stabilizers. Ethnopharmacology study may lead to new bioactive substances for drug design for allergy therapeutics. In our previous study, several natural phytochemicals e.g. flavonoids, stilbenes, coumarins,phenols etc are identified as nutraceuticals in allergic reactions. In Type I hypersensitivityreaction, binding of immunoglobulin E (IgE) with its high affinity receptor (FcεRI) on mast cell,plays a significant role in allergic reaction. Molecular docking studies provides detailed molecular level interaction between IgE with FcεRI receptor in presence and absence of four procyanidin molecules, present in apple. Decrease in binding energy and conformational change in ε subunit of FcεRI receptor occur in presence of procyanidin C1. This conformation change can affect the signal transduction pathway in mast cell degranulation. This in-silico study has shown that procyanidins present in apple can act as mast cell stabilizers by changing the binding affinity of IgE with its receptor FcεRI during allergic reaction.

Cite this article: Basu A, Sarkar A, Basak P. Immunoinformatics Study of Procyanidins as Mast Cell Stabilizers. Pharmacog J. 2018;10(4):814-7.