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3D QSAR AND MOLECULAR DOCKING STUDIES OF FLAVONOIDS AS SPLEEN TYROSINE KINASE INHIBITORS

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ABSTRACT: Spleen tyrosine kinase (Syk) is a member of tyrosine kinase family protein. Syk protein plays a vital role during intracellular signal transduction from high affinity IgE receptor ($F_{c\varepsilon}RI$) in allergic reaction. Flavonoids are well known compounds for their anti-allergic properties. In this present work, thirty-four structurally similar flavonoids are investigated as Syk inhibitors by using 3-dimensional quantitative structure-activity relationship (QSAR) models and molecular docking studies. By applying genetic algorithm (GA) method, different types of 3D-MoRSE descriptors are selected from various types of geometrical descriptors for model building. A Multiple Linear Regression is built up, considering the inhibitory effect of seventeen flavonoids on model mast cells by QSARINS software. The model is validated internally using the Q^2_{LOO} criterion in leave-one-out method. William graph and Insubria graph are plotted to identify the application domain for that model. The same model is also externally validated for other seventeen flavonoid compounds. Docking studies of these thirty-four compounds are also performed using AutoDock to identify interacting amino acids of Syk protein. Docking analysis reveals that flavonoid chrysin depicts lowest binding energy, -2.74 with Syk protein. Methoxy substitution causes adverse effect on binding. The flavonoid chrysin is found in carrot. Pharmacokinetics study of chrysin shows that the gastrointestinal absorption of chrysin is high with bioavailability score of 0.55. The current work will help in drug design of human Syk inhibitors and provides information for molecular level of interactions between Syk and the flavonoid group of compounds.

INTRODUCTION: The spleen tyrosine kinase Syk is a tyrosine kinase protein, which is involved in signal transduction in hematopoietic cells, as well as non-hematopoietic cells. In first type of cells, it plays crucial roles in normal function of B and T cells, neutrophils, macrophage, aggregation of platelets and cell signalling in mast cells of origin and plays a crucial role in signalling in most of these cells.

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It is involved in B and T-cell functions, platelet aggregation, mast cell signalling, neutrophils and macrophages [1, 2]. The activity of Syk protein as tumor suppressor is an example of its function in second type of cells.

From this point of view, Syk has been introduced as a target for a new type of anticancer drugs in breast cancer, overian cancer [3]. Syk kinase inhibitor is also used in treatment of rheumatoid artharitis [4], lupus nephritis [5], vascular diseases [6], allergic asthma and rhinitis [7]. When antigens bind to immunoglobulin E (IgE) during allergic reaction, mast cells and basophils are activated to release inflammatory mediators *e.g.* histamine, prostaglandin, leukotriens, serotonin *etc*. In both early- and late-phase allergen-induced type I hypersensitivity reactions, Syk protein inhibitor completely blocks serotonin mediator release from mast cell [8]. Syk binds with FcεRI, the high affinity receptor for IgE, for degranulation in mast cells [1]. Activation of tyrosine kinases plays the most important role during transmission of downstream signalling events in mast cells. This signal transduction pathway is required for the regulation of mast cell degranulation [9].

There are several compounds *e.g.* triazolopyridine [10], fostamatinib [11], 6- [(1R, 2S)- 2- Amino- cyclo-hexylamino]- 4- (5, 6-dimethyl-pyridin-2-ylamino)-pyridazine-3-carboxylic acid amide [12] and a series of pyrazolopyrazine- 3- amine and pyrazolo-pyrimidine-3-amine derivatives [13], which are synthesized and screened as Syk protein inhibitors in various immunological processes.

In this work, ethanopharmacological drugs are investigated as potential mast cell stabilizers. Several natural constituents, which are obtained from different herbs, like Holy Basil (*Ocimum tenuiflorum*) [14], Chamomile (*Matricaria recutita*) [15], kaempferol in *Cerbera manghas* [16], grapeseed extract [17], polyphenols of red wine [18] are identified as mast cell stabilizers. Different types of chemical compounds are also analysed as natural mast cell stabilizers like flavonoids, stilbenes, curcuminoids [19]. Numerous flavonoids like luteolin, apigenin, quercetin, fisetin, myricetin, morin, naringenin *etc*. are tested as Syk protein inhibitors during mast cell degranulation reaction [20, 21]. Inhibitory effects of those flavonoids along with their structural requirements for antigen - induced degranulation process is estimated [22].

The role of Syk protein in mast cell degranulation reaction will be cleared only when potent, specific inhibitors of Syk are identified and evaluated in clinical trials. To do so we perform Quantitative Structure-Activity Relationship (QSAR) analysis to study the human spleen tyrosine kinase inhibitory activity of a series of flavonoid compounds. The QSAR study is based on the important chemistry principle, which states that similar compounds have similar biological properties [23]. The biological activity of the chemical compounds has correlation with their physicochemical properties, which are known as molecular descriptors [24]. Recently QSAR models are developed for new drug designing in cancer therapy [25] and anti-HIV therapy [26]. We use the QSARINS software [27] for building a Multiple Linear Regression (MLR) model to recognize a potential flavonoid as Syk protein inhibitor.

In new drug designing study, molecular docking analysis between various ligands and the protein of interest, is gaining huge interest nowadays. In docking study, the binding energy of docked compound helps to determine the strength of interactions between ligand and protein. As an example of ethanopharmacological study, several ligands from *Cassia tora*, *Brassica campestris* and *Calotropis procera*, are targeted against acetylcholinesterase using molecular modelling and docking studies for drug therapy in Alzheimer's disease [28]. In a similar approach we perform the molecular docking study with flavonoid compounds with Syk protein by utilizing AutoDock 4.2.3 molecular docking software [29].

Bioavailability of herbal medicinal product is an assessment of several features *e.g.* degree of absorption after administration, digestion, elucidation of metabolic pathways (yielding potentially new active compounds), and the assessment of elimination routes and their kinetics [30]. Bioavailability of these natural flavonoids must be considered to determine their pharmacological efficiency as mast cell stabilisers [31]. This information is very relevant for good understanding of the concentrations that will be achieved in the body after administration of those flavonoids as Syk inhibitor. Using Swiss ADME [32, 33], a web tool we evaluate pharmacokinetics, drug-likeness of flavonoids.

MATERIALS AND METHODS:

Data Set for QSAR Study of Syk Inhibitor: The first step in QSAR model construction is to collect

a list of flavonoid compounds with experimentally determined inhibitory activity data. The inhibitory effects of 34 flavoniods on the release of β-hexosaminidase from model human cells are compiled from experimental data [22]. Their 2D chemical structures are shown in **Fig. 1**. The data set of 34 experimental flavonoid compounds is divided into training set for model generation, and a prediction set (marked with * in **Table 1**) for model validation, both containing 17 compounds. The chemical structures of flavonoids as SMILES format are retrieved from PubChem database [34]. The biological activity (IC_{50}) of the molecules are converted to their corresponding pIC_{50} values, and used as dependent variables in the QSAR calculations **Table 1**.

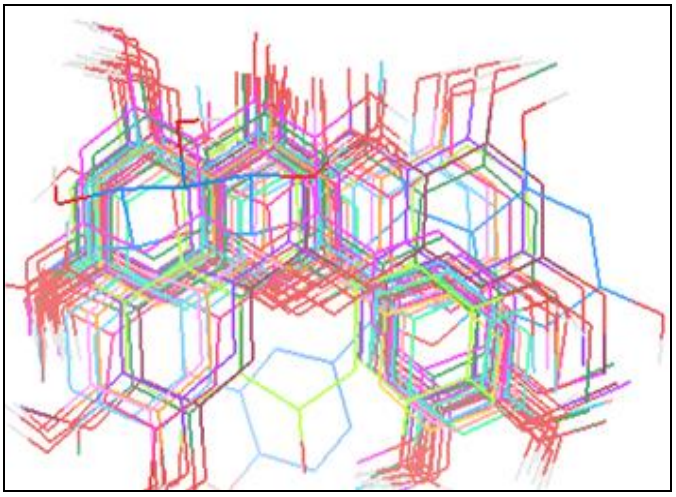

FIG. 1: TWO DIMENSIONAL STRUCTURES OF THIRTY - FOUR FLAVONOID COMPOUNDS

TABLE 1: LIST OF FLAVONOIDS WITH THEIR INHIBITORY ACIVITY

Compound no.	Name of Flavonoids	CID no	IC_{50}	pIC_{50}
1	Flavone	10680	44	-1.64397
2	7-Hydroxyflavone	5281894	33	-1.51185
3	5,7-Dihydroxyflavone (Chrysin)	5281607	20	-1.30103
4	5-Hydroxy-7-methoxyflavone (Tectochrysin)	5281954	49	-1.69037
5	7,4'-Dihydroxyflavone	5282073	22	-1.34294
6	3',4' Dihydroxyflavone	145726	30	-1.47756
7	Baicalein(5,6,7-Trihydroxyflavone)	5281605	16	-1.20412
8	Wogonin	5281703	29	-1.46218
9	Apigenin	5280443	6.1	-0.78542
10	3',4',7 Trihydroxyflavone	5322065	13	-1.11407
11	Luteolin (3',4',5,7-Tetrahydroxyflavone)	5280445	3	-0.47716
12	Diosmetin	5281612	2.1	-0.32221
13	Pilloin (3',5-Dihydroxy-4',7-dimethoxyflavone)	5320496	28	-1.44733
14	5-Hydroxy-3',4',7-trimethoxyflavone (7,3',4'-tri-O-methylluteolin)	5272653	19	-1.27901
15	3',4',5,7-Tetramethoxyflavone (5,7,3',4'-Tetramethylluteolin)	631170	68	-1.83268
16	3-Hydroxyflavone	11349	69	-1.83863
17	Kaempferol	5280863	14	-1.11463
18	Fisetin*	5281614	3	-0.4771
19	Quercetin*	5280343	4.6	-0.6627
20	Quercetin 3-O-Glc*		54	-1.7324
21	Rhamnetin (7-Methoxyquercetin)*	5281691	21	-1.3222
22	Tamarixetin (4'-Methoxyquercetin)*	5281699	57	-1.7559
23	Ombuin (4',7-Dimethylquercetin)*	5320287	5.5	-0.7404
24	3,7-Di-O-methylquercetin (3',4',5-Trihydroxy-3,7-dimethoxyflavone)*	5280417	64	-1.8062
25	Ayanin (3,7,4'-Tri-O-methylquercetin)*	5280682	18	-1.2553
26	3',4',7-Trimethylquercetin*	5748558	6	-0.7781
27	Retusin (Quercetin-3,7,3',4'-tetramethyl ether)*	5352005	25	-1.3979
28	Myricetin*	5281672	23	-1.3617
29	Mearnsetin*	10359384	27	-1.4314
30	7 methoxy myricetin (Europetin; 7-O-methylmyricetin)*	44259636	19	-1.2788
31	3,7 dimethoxy myricetin (3,7-dimethylmyricetin)*	24721651	27	-1.4314
32	4',7 dimethoxy myricetin (Myricetin 7,4'-dimethyl ether)*	44259638	7.9	-0.8976
33	3',4',7 trimethoxy myricetin (Myricetin 7,3',4'-trimethyl ether)*	12532439	13	-1.1139
34	3,5,7,3',4',5' hexamethoxy myricetin (Hexa-O-methylmyricitin)*	634113	58	-1.7634

Energy Minimization of Ligand Molecules: Energy minimized structure of 34 ligand molecules are obtained using MM2 force field [35] with minimum RMS gradient 0.01.

Molecular Descriptors Calculation: Using energy minimized structures, molecular descriptors are calculated using ChemDes [36].ChemDes is a free web-based platform for the calculation of molecular descriptors and fingerprints, which provide more than 3,679 molecular descriptors that are divided into 61 logical blocks. Among them 3D ChemoPy molecular descriptors [37] *e.g.* geometric descriptors (12), CPSA descriptors (30), RDF descriptors (180), WHIM descriptors (70), MoRSE descriptors (210) are calculated for each flavonoids.

QSAR Model Construction and Validation: In order to obtain the MLR model, we use the QSARINS software [27] and a genetic algorithm (GA) method is applied to select relevant set of variables from a large number of descriptors (502). Variables are specified with 10 models per size with 0.050 cut off according to QUIK rule [38]. The genetic algorithm is set up with population size 200, 2000 generations per size and mutation rate is 20. For selecting the best model with two descriptors, models are arranged by QSARINS, according to R^2 (the highest value correlates with the good fitness of the model, Q^2 LOO (the highest value indicates the robustness of the model).

Syk Protein 3D Structure Identification: Here, the X-ray diffraction crystallographic structure of human Spleen Tyrosine Kinase with resolution 1.9Å (EC#: 2.7.10.2) is extracted from Protein Data Bank with PDB ID 4FL3 [39]. This protein is prepared as receptor by using the graphical interface of the AutoDock Tools, which is present in the MGL Tools 1.4.6 program [29] by using Chem Office Professional 16 suite. All 34 inhibitors are prepared for docking studies by the same programme in the pbdqt format.

Docking Studies: In docking studies, a 60 X 60 X 60 box with a grid spacing of 2 Å is used. The centroid of the grid map has been set (0, 0, 0) with the coordinates along x, y and z axis. No. of individuals in population is 50, for 1000 generations. The maximum no. of docking is set to 20 with energy evaluations 2500. Docking results are analysed with their binding energies in dlg format by Python Molecule Viewer version 1.5.6 [40].

RESULT AND DISCUSSION:

Best QSAR Model Using MLR: By using user friendly QSARINS software [27], we develop different QSAR models with low multi-collinearity between molecular descriptors and good correlation with the biological response. The best MLR model for training set is built up with 3D molecular descriptors namely Molecule Representation of Structures based on Electron Diffraction (MoRSE) and Charged Partial Surface Area descriptor (CPSA). The QSAR model and its statistical parameters are shown below:

QSAR Equation:

$\log(1/IC_{50})$ = - 0.0817 (± 1.4970) MoRSEV5 - 0.0433 (± 0.0179) PNSA3 - 3.2940 (± 0.6482)

Where, MoRSEV5 means Molecule Representation of Structures based on Electron Diffraction signal 05, weighted by atomic van der waals volumes, PNSA3 means atomic charge weighed negative surface area.

N= 17; R^2= 0.8737; R^2_{adj} = 0.8557; R^2-R^2_{adj} = 0.0180; LOF = 82.8709; K_{xx} = 0.6603; Delta K = 0.0090; $RMSE_{tr}$ = 6.9614; MAE_{tr} = 5.3576; RSS_{tr} = 823.8344; CCC tr =0.9326; s = 7.6711; F = 48.4212

Here, N is the number of compounds of the training set, R^2 is the coefficient of determination, R^2_{adj} is adjusted R^2, s is standard error of estimate, F is variance ratio, LOF is Friedman lack of fit [41, 42], Kxx is the correlation among descriptors [38], Delta K is the difference of the correlation between the descriptors (Kx) and the descriptors plus the responses (Kxy), $RMSE_{tr}$ is Root Mean Square Error in fitting (for training set), MAE_{tr} is Mean Absolute Error in fitting (calculated on training set), RSS_{tr} is Residual Sum of Squares in fitting (also for training set) and CCC_{tr} is the concordance correlation coefficient calculated over the training set [43, 44, 45]. The model projects an R^2 value is of 0.8737, which means a proper fitness for modelling Syk protein inhibition.

In addition, an R^2_{adj} value of 0.8557, which indicates that it is convenient to add a new descriptor with the model. Similarly, along with the low value of the Kxx (0.6603), we can say that the correlation between the model descriptors is low. Not only that the Delta K parameter has 0.0090 value which is indicative of good correlation between selected descriptors and the inhibitory response, with negligible error on experimental and calculated parameters ($RMSE_{tr}$ = 6.9614; MAE_{tr} = 5.3576; s = 7.6711). The scatter plot of experimental versus predicted activity by model equation is shown in **Fig. 2**.

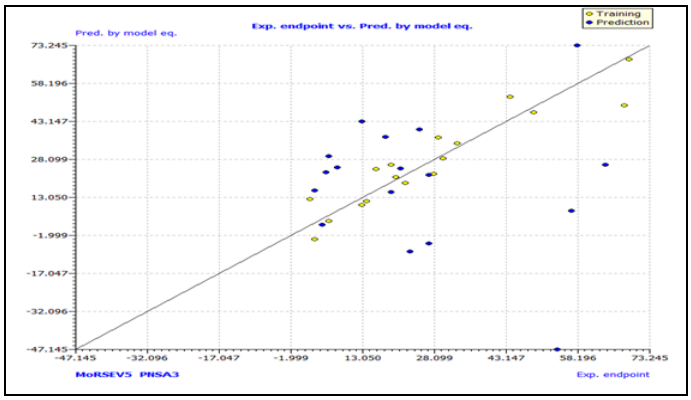

FIG. 2: SCATTER PLOT OF EXPERIMENTAL IC_{50} VERSUS PREDICTED VALUES BY OSAR MODEL

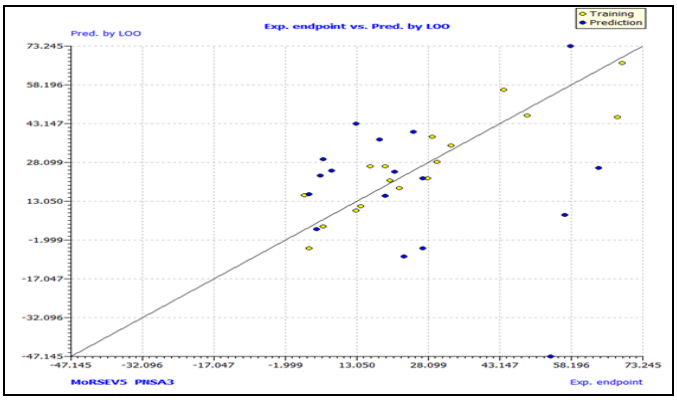

FIG. 3: THE VALUES PREDICTED BY LOO VERSUS THE EXPERIMENTAL IC_{50} VALUES

Model Validation: In internal validation procedure, our model is validated for fitting and stability by using the statistical parameters of cross-validation Leave-one-out (LOO). The value of Q^2_{LOO} is 0.8096 which is comparable with the value of R^2 (0.8737). The QSAR model is robust considering the values of $RMSE_{cv}$ = 8.5463, MAE_{cv} = 6.5591, CCC_{cv} = 0.8990. In **Fig. 3**, biological activity values predicted by LOO versus the experimental values are shown (yellow circles for training and blue circle for prediction).

External Validation: In QSAR studies, the predictions of compounds present within the applicability domain (AD) are considered as dependable [46]. William graph is plotted with leverage and standardized residuals [47] in **Fig. 4**. From this figure, it can be concluded that plot compound 30 and 33 are present outside the limit of critical leverage (h = 0.529). In another approach for detecting the model applicability domain using Insubria plot not only compounds 33 and 30, but also compound 34 are marginally present outside the applicability domain as shown in **Fig. 5**.

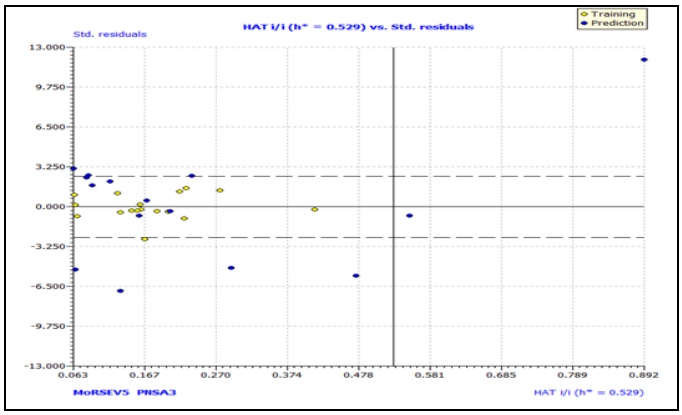

FIG. 4: WILLIAMS PLOT WITH HAT DIAGONAL VALUES VERSUS STANDARDIZED RESIDUALS

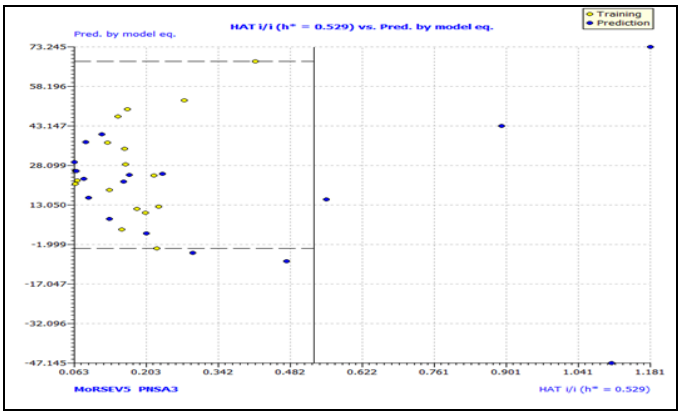

FIG. 5: INSUBRIA PLOT WITH APPLICABILITY DOMAIN

Molecular Docking and Visual Representation of Protein - Ligand Binding: Using AutoDock 4.2.3 software, binding energies of all 34 compounds in our dataset are calculated. Analysing the docking results, the compound 3 *i.e.* flavonoid chrysin (compound 3) is selected with the lowest

binding energy (-2.74 kcal/mol) as most suitable flavonoid in Syk inhibition. As shown in **Fig. 6**, the flavonoid chrysin is present within a binding pocket region, forming hydrogen bonding with Gly 190, Lys 191 and His 209. Hydroxyl (OH) group at position 7 shows stabilizing interaction with basic amino acid residues Lys and His. Other compounds containing 7 OH group *e.g.* 3', 4', 7 Trihydroxyflavone, Wogonin also shows strong binding interaction with Syk protein. On the contrary, flavonoids substituted with methyl group causes unfavourable effect on protein - ligand binding depicted in their binding energy.

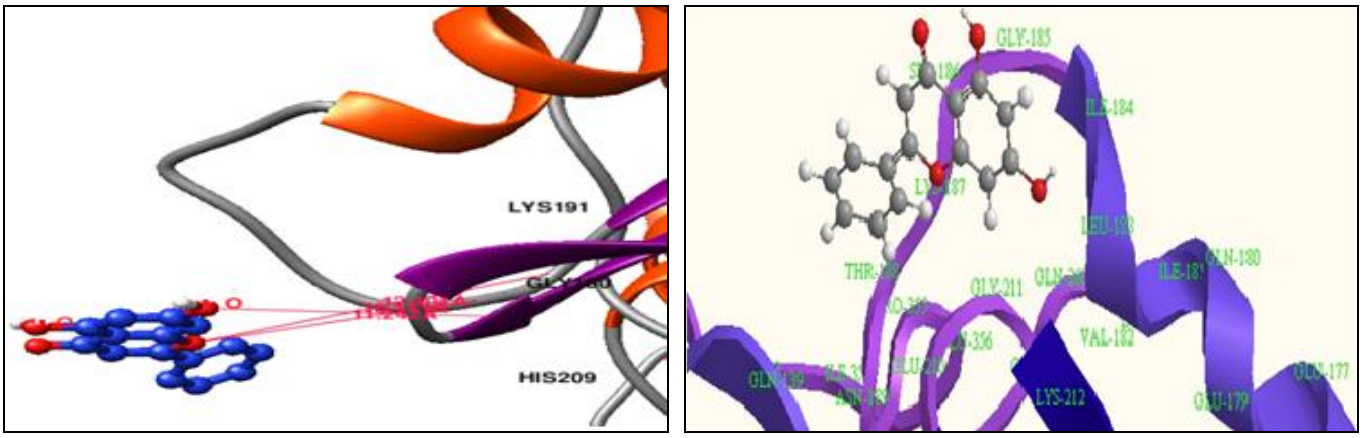

FIG. 6: DOCKING STRUCTURE OF COMPOUND 3, CHRYSIN WITH Syk PROTEIN

Bioavailability Predication: From Swiss ADME [33], comparing pharmacokinetic data, it can be concluded that chrysin, 3', 4', 7 Trihydroxyflavone and Wogonin are highly absorbed by GI tract. Drug likeness of all these three compounds is positive with zero violation in Liponski rule.

CONCLUSION: In our earlier work, we have identified carboxamidotetrazole derivatives of furan, thiophene, naphthalene and benzothiophene can act as potent mast cell stabilisers on human basophils [48]. In our present study, by using QSAR model with MLR equation and molecular docking analysis, we want to highlight the anti-allergic effect of flavonoids as human spleen tyrosine kinase) Syk protein inhibitor. Two 3D molecular descriptors *e.g.* MoRSEV5 and PNSA3 are selected by genetic algorithm (GA).

The first one weights the atomic van der waals volumes of flavonoid compounds. The second one is related with solvent accessible surface area and partial charge of all negatively charged atoms *e.g.* oxygen atom of hydroxyl groups of flavonoids. From the molecular docking studies of all 34 flavonoids, the interaction between hydroxyl groups in 7 position of flavonoids are identified. 3', 4', 7 Trihydroxyflavone is present in Broad bean pod, ladino clover, Alfalfa and rhizome part of glycyrrhizae radix. Chrysin is present in carrot, alfalfa, parsley and thyme [49]. These compounds are recognized as ethano-pharmacological drugs as mast cell stabilizers in allergic treatment.

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CONFLICT OF INTEREST: The authors have no conflict of interest.

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