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PREDICTIVE QSAR ANALYSIS OF FLAVONOID ANALOGUES AS ANTIPSORIATIC AGENTS

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ABSTRACT: Objective: Newly designed antipsoriatic agents which are substituted series of analogues of flavonoids (kaempferol and quercetin) that belong to the subclass flavonols were subjected to (2D-QSAR) analysis using VLIFEMDS-QSARPro software with an intention to derive and understand the possible correlation of biological activity as dependent variable and other descriptors like molecular weight, XLogP values as independent variables. It can be concluded that the current study provides better insight for designing and chemical synthesis of more potent antipsoriatic agents. **Methods:** Several statistical regression expressions were obtained using variable selection method as simulated annealing coupled with various model building methods like partial least squares (PLS) Regression, multiple linear regression (MLR) *etc*. **Results:** For the analogues of both quercetin and kaempferol, a total of 9 QSAR models were generated, each using test set of 15 and training set of 45 similar compounds. The best QSAR model generated by PLS model building method for quercetin was model Q4 with correlation coefficient r^2 of 0.9021 and significant cross validated correlation coefficient q^2 of 0.5791.Similarly, the best QSAR model generated by MLR method, for kaempferol was model K2 with r^2 of 0.687, significant q^2 of 0.5676. Both model Q4 and K2, gave significant results and revealed that presence of SdOE-index, SdsCH count favours the biological activity of quercetin analogues whereas presence of SdssCE-index contributes positively towards biological activity of analogues of kaempferol. This study suggests that such descriptors will be helpful in designing more potent antipsoriatic agents.

INTRODUCTION: Psoriasis is one of the most common chronic, inflammatory and non-contagious autoimmune skin diseases that produces dry flakes as plaques of thickened, scaling skin. The dry flakes are thought to result from the excessively rapid proliferation of skin cells that is triggered by inflammatory chemicals produced by lymphocytes [1].

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The disease is considered as a T- cell mediated immune response characterized by hyper proliferative keratinocytes coupled with infiltration of T cells, dendritic cells, macrophages and neutrophils [2].

The several subsets of T cells each have a distinct function. T-helper cell (TH1 and TH2) initiate production of defining cytokines whereas IFN-γ and interleukin (IL)-4 are essential for initiating psoriatic lesions [3, 4]. T_H cells assist other white blood cells in immunological processes, including maturation of B cells into plasma cells, memory B cells along with activation of cytotoxic T cells and macrophages.

These cells are also known as $CD4^+$ T cells because they express the CD4 glycoprotein on their surfaces. TH cells become activated when they are presented with peptide antigens by MHC class II molecules, which are expressed on the surface of antigen-presenting cells (APCs).Once activated, they divide rapidly and secrete small proteins called cytokines that regulate in the active immune response. These cells can differentiate into one of the subtypes, including T_H1, T_H2, T_H3, T_H17, T_H9, or T_{FH}, which secrete different cytokines to facilitate different types of immune responses. Signalling from the Antigen Presenting Cells (APC) directs T cells into particular subtypes [5].

There are many reported drug targets in psoriasis like STAT3, p53, Caspases *etc*. Out of which one is a protein called calcineurin (CaN), which is also protein phosphatase 2B (PP2B) [6]. It is a ubiquitously expressed Ca^{2+}-dependent cytosolic Ser/Thr protein phosphatase and is highly conserved in eukaryotes [7]. Cyclosporin A (CsA) is molecule of choice for treatment of psoriasis. CsA is a potent immune suppressant that induces its biological effects by forming an initial complex with cytosolic proteins termed immunophilins. These drug immunophilin complexes then bind to and inhibit the serine/threonine protein phosphatase calcineurin (CaN) [8].

CaN seems to be the only protein phosphatase that dephosphorylates NFATc (nuclear factor of activated T cells) [7]. Upon stimulation of T cells and subsequent calcium mobilization, activated calcineurin dephosphorylates NFATc (at 13 serine residues in the regulatory region), leading to its nuclear translocation by exposure of the nuclear localization sequence [8]. Concerted rephos-phorylation of NFATc leads to its translocation into cytosol and abrogation of NFATc transcriptional activity. CaN not only modulates the activity of NFATc but also several other transcription factors such as NF-κB, AP-1, and Elk1 [1]. The inhibition of calcineurin activity is so far the only effective therapeutic strategy to suppress the activation of memory $CD4^+$ and $CD8^+$ T cells and their proliferation that plays an important role in initiation of psoriasis [1, 4].

CsA is considered as a classical drug targeting calcineurin activity and subsequently inhibiting NFATc activation in onset of psoriasis [7]. It is one of the few drugs suppressing not only the activation of naïve and effect or T_H cells but also the memory T_H cells [9]. The efficacy of CsA has been used as a powerful argument to support the fundamental role of T cells in the pathogenesis of psoriasis [10]. Systemic use of CsA is effective in treatment of psoriasis. However, its usage is restricted by serious side-effects such as nephro- and neuro-toxicity. Over the past 2 decades, considerable progress has been made in further elucidating the complex pathogenesis of psoriasis which will hopefully facilitate the development of a new armamentarium of more effective, targeted therapies [11]. Despite these important advances, substantial gaps remain in our understanding of psoriasis and its treatment, necessitating further research [12].

Herbal Drugs may be developed as an alternative control medication without the harmful side effects known to be associated with drugs like CsA. Flavonoids of herbal or synthetic origin are reported to exhibit various anti-inflammatory properties [13]. Flavonoids are hydroxylated phenolic substances and are known to be synthesized by plants in response to microbial infections [14]. Activities of flavonoids are structure dependent and they have been shown to have an ability to induce human protective enzyme systems [15]. A number of studies have suggested protective effects of flavonoids against many infectious bacterial, viral diseases and degenerative diseases such as cardiovascular diseases, cancers and other age-related diseases, *etc* [15, 16]. Kaempferol and quercetin are flavonoids that belong to the subclass flavonols [14, 15] and are reported to inhibit the phosphatase activity by binding to the catalytic domain of calcineurin and act independently of any matchmaker protein. Kaempferol suppresses IL-2 gene expression in Jurkat T cells [17]. Surprisingly, it also inhibits the calcineurin-independent TNFα-induced NF-κB activation in HEK293 cells [1].

***In silico* Analysis:** A new field of *in silico* protein modelling and novel drug designing has become available which considerably saves time and efforts by identifying potential drug targets *via* bioinformatics tools [18]. The *in silico* tools can be used to analyze the target protein structures for possible binding sites and generate candidate drug

which can bind effectively to target [19]. Various softwares are designed to suit this approach such as modelling environment of Schrödinger Maestro, Discovery Studio, VLIFEMDS, *etc* [20]. New substituted series of analogues have been designed using Maestro 11 modelling interface of Schrödinger software (https://www.schrodinger.com/maestro) [21]. Maestro 11 is powerful and versatile molecular modelling environment software and is the linchpin of Schrödinger's computational technology. Maestro 11 has a vast array of visualization options making it possible to glean molecular properties as well as detailed intermolecular interactions. It is the portal to the most advanced science in computational chemistry [22].

QSAR: Quantitative structure-activity relationship (QSAR) (sometimes QSPR: quantitative structure property relationship) is the process by which a chemical structure is quantitatively correlated with a well-defined process, such as biological activity or chemical reactivity. It is based on the fact that biological activity of a compound is a function of its physicochemical parameters, *i.e.* physical properties, such as molecular weight, solubility, surface tension, partition coefficient and chemical properties such as dissociation or ionization, electron density, and rate of hydrolysis, *etc* [23]. There are two main objectives for the development of QSAR: Development of predictive and robust QSAR, with a specified chemical domain, for prediction of activity of untested molecules and it can also act as an informative tool by extracting significant patterns in descriptors related to the measured biological activity leading to understanding of mechanisms of given biological activity. Such information could help in suggesting designing of novel lead molecules with improved activity profile [24, 25].

The quantitative approach in QSAR depends upon expression of a structure by numerical values and then relating these values to the corresponding changes in the biological activity by using statistical methods. The QSAR is also an important tool to study role of various physicochemical properties of a drug in providing necessary biological activity. There is a wide choice of relevant paid and free software tools for developing QSAR models like VLIFEMDS, Schrödinger, Vega, *etc* [24 - 26]. The QSAR based modelling uses variety of statistical regression methods for prediction of various structure activity models based on descriptors like molecular weight, XLogP, type of hydrogen bond donor, acceptor *etc* [27]. multiple linear regression (MLR), partial least squares (PLS) and principle component regression (PCR) are widely used statistical regression methods. This bioinformatics based approach is expected to help in gaining better insight to predict the biological activity for new analogues [25, 26].

The VLIFEMDS-QSARPro (www.vlifesciences.com) is an exhaustive regression analysis tool and has the prediction facilities for biological activities of newly designed analogues. It also comes with powerful pack of facilities for quantitative structure activity relationship analysis, statistical modelling, activity / property prediction and visualization [24-26]. This software performs descriptor calculations, rapid calculation of more than 1000+ descriptors like 2D, 3D, alignment independent, graphical representation of relative distribution of descriptor values by distribution and pattern plot and cross-correlation matrix. In addition, VLIFE-QSARPro offers wide choice of methods for drug variable selection and model building. Any of the variable selection methods with any of the model building methods can be coupled *e.g.* simulated annealing variable method with statistical model building methods such as MLR, PCR and PLS [28].

2D QSAR models are based on descriptors derived from a 2D graph representation of a molecule. Such models are generated using training and test set molecules with uniformly distributed biological activities. The observed selection of test set molecules is made by considering the fact that test set molecules will represent a range of biological activity similar to the training set [24].

Biological Activity: Any structure and activity study is based on the assumption that there is an underlying relationship between the molecular structure of the compound and its biological activity. The QSAR analysis is an attempt to establish a correlation between various molecular properties of a set of molecules with their experimentally known biological activity. A dataset of a series of synthesized molecules tested for its desired biological activity is needed for carrying

out the QSAR analysis. The quality of the predicted model is totally dependent on the quality of the experimental data used for building these models. Biological activity for the purpose of QSAR studies can be of two types: 1) Continuous Response: MEC, IC_{50}, ED_{50}, % inhibition 2) Categorical Response: Active / Inactive. Also to have confidence in QSAR analysis, biological data of at least 20 molecules is recommended [24].

Descriptor Calculation: Good descriptors should characterize molecular properties important for molecular interactions – Hydrophobic, electronic, steric / size / shape, hydrogen bonding. The handbook of molecular descriptors published in the year 2000 describes more than 2000 molecular descriptors used in QSAR and molecular modelling [29]. The VLIFEMDS-QSARPro software has been employed for the calculation of different 2D descriptors. There are three categories of descriptors like thermodynamic parameters which describe free energy change during drug receptor complex formation, spatial parameters are the quantified steric features of drug molecules required for its complimentary fit with receptor and electronic parameters deal with weak non-covalent bonding between drug molecules and receptor. Some example of descriptors are XlogP, logP, hydrophobicity, elemental count, path count, chain count, path cluster count, molecular connectivity indices, *etc*. The calculated descriptors are to be gathered in a data matrix for selection of test and training set [27, 30].

Selection of Training and Test Set: In order to obtain a validated QSAR model for the purpose of meaningful prediction, an available dataset should be divided into the training and test sets. For the prediction statistics to be reliable, the test set must include at least five compounds. Ideally, the division into the training and test set must satisfy the following three conditions: (i) All representative compound-points of the test set in the multidimensional descriptor space must be close to those of the training set. (ii) All representative points of the training set must be close to those of the test set. (iii) The representative points of the training set must be distributed within the whole area occupied by the entire dataset [24]. Following are some of the methods for division of the dataset into training and test set: 1) Manual Selection: This is done by visualizing the variation in the chemical and biological space of the given dataset. 2) Random Selection: This method creates training and test set by random distribution. 3) Sphere Exclusion Method: This is a rational method for creation of training and test set. It ensures that the points in the both the sets are uniformly distributed with respect to chemical and biological space. 4) Other methods like experimental design using for example, full factorial, fractional factorial and Onion Design *etc* [31, 32].

Variable Selection Method: The QSAR regression methods help to shortlist important descriptors which play an important role in determining biological activity of structures. These methods are divided mainly into two categories: 1) Systematic variable selection: These methods add or delete a descriptor in steps, one-by-one, in the model and the addition can be stepwise forward or stepwise forward-backward or stepwise backward 2) Stochastic variable selection: These methods are based on simulation of various physical or biological processes [33]. These methods create model starting from randomly generated models and later modifying these models by using different process operators (*e.g.* perturbation, crossover *etc*.) to get better models. Various stochastic variable selection methods are available and one can choose the appropriate one like simulated annealing, genetic/evolutionary algorithms or a user defined selection method [24]. The results obtained with any variable method further are subjected to construction of 2D and 3D QSAR models by coupling with appropriate statistical model building methods like MLR, PCR or PLS to generate QSAR models [28, 34].

Multiple Linear Regressions (MLR): It is widely used method for building QSAR models. MLR models have been developed as a mathematical equation which can relate chemical structure to the activity. The results obtained could be helpful to pharmacologists and medicinal chemists to come up with improved drugs like antipsoriatic agents [35]. This method has been used for modelling linear relationship between a dependent variable Y (IC_{50}) and independent variable X (2D descriptors). MLR is based on least squares calculations where sum-of-squares of differences of observed and a

predicted value is minimized to achieve a better model. MLR estimates values of regression coefficients (r^2) by applying least squares curve fitting method [28, 34]. The resultant model creates a relationship in the form of a straight line (linear) that best approximates all the individual data points. In regression analysis, conditional mean of dependent variable (IC_{50}) Y depends on (descriptors) X. MLR analysis extends this idea to include more than one independent variable.

Regression equation takes the form: b1x1 + b2x2 + b3x3 ---------(i)

Where Y is dependent variable, 'b's are regression coefficients for corresponding 'x's (independent variable), 'c' is a regression constant or intercept [36].

Principal Component Regression Analysis (PCR): It is a data compression method based upon the correlation among dependent and independent variables. PCR provides a method for finding structure in datasets. Its aim is to group correlated variables, replacing the original descriptors by new set called principal components (PCs) [37]. These PCs are uncorrelated and built as a simple linear combination of original variables. It rotates the data into a new set of axes such that first few axes reflect most of the variations within the data [38]. PCA selects a new set of axes for the data. These are selected in decreasing order of variance within the data. Purpose of principal component PCR is the estimation of values of a dependent variable on the basis of selected PCs of independent variables [37, 39].

Partial Least Squares Regression (PLS): It is a popular regression technique which can be used to relate one or more dependent variable (Y) to several independent (X) variables [40]. PLS relates a matrix Y of dependent variables to a matrix X of molecular structure descriptors. PLS is useful in situations where the number of independent variables exceed the number of observations, when X data contain collinearities or when N is less than 5 M, where N is number of compounds and M is number of dependent variable. Main aim of PLS regression is to predict the activity Y from X and to describe their common structure [41].

Model Validation: Model validation is a process to test the internal stability and predictive ability of the QSAR models [39]. Developed QSAR models have been validated by some procedure as follows:

Internal validation is carried out using leave one-out (LOO - Q2) method. For calculating, each molecule in the training set is to be eliminated once and the activity of the eliminated molecule predicted by using the model developed by the remaining molecules. That q^2 is calculated using the equation which describes the internal stability of a model [27, 40].

$$Q^2 = 1 - \frac{\sum(Y_{pred} - Y_{abc})^2}{\sum(Y_{abc} - Y_{mean})^2} \text{ ------(ii)}$$

In Eq. (ii), Y_{pred} and Y_{abc} indicate predicted and observed activity values respectively and Y_{mean} indicate mean activity value. A model is considered acceptable when value of Q^2 exceeds 0.5.

For external validation, the activity of each molecule in the test set is predicted using the model developed by the training set. The pred_r^2 value is calculated as follows:

$$pred\_r^2 = \frac{\sum(Y_{pred(test} - Y_{test})^2}{\sum(Y_{train} - Y_{mean(train)})^2} \text{ -----(iii)}$$

In Eq (iii) $Y_{pred\ (test)}$ and Y_{test} indicates predicted and Y_{train} observed activity values respectively of the test set compounds and indicates mean activity value of the training set. For pred_r^2 value should be more than 0.5, which signifies that predicted model can be taken for further analysis [39].

Randomization Test: Randomization test or Y-scrambling is important popular mean of statistical validation. To evaluate the statistical significance of the QSAR model for an actual dataset, one tail hypothesis testing is commonly used. The robustness of the models for training sets is examined by comparing these models to those derived for random datasets. Random sets are generated by rearranging the activities of the molecules in the training set. The statistical model is derived using various randomly rearranged activities (random sets) with the selected descriptors and the corresponding q^2 are calculated. The significance of the models hence obtained is derived based on a calculated Z_{score}.

A Z score value is calculated by the following formula: = Z_{score} = h-μ/σ ---------- (iv)

Where h is the q^2 value calculated for the actual dataset, μ the average q^2 and s is its standard deviation calculated for various iterations using models build by different random datasets. The probability (a) of significance of randomization test is derived by comparing Z score value with critical Z score value as reported, if Z score value is less than 4.0; otherwise it is calculated by the formula as given in the literature. For example, a Z score value greater than 3.10 indicates that there is a probability (a) of less than 0.001 that the QSAR model constructed for the real dataset is random. The randomization test suggests that all the developed models have a probability of less than 1% that the model is generated by chance [30, 32, 38].

The present work was undertaken because currently there are very few drugs available for the treatment of the debilitating psoriasis disease and there is a need to quickly identify the substituted analogues of promising phytochemical compounds using *in silico* approach that may help to identify novel compounds having potential biological activity and less side effects. The promising analogues predicted may then be actually synthesized in the laboratory and evaluated using *in vitro* and *in vivo* testing methods. The objective of the present work was to perform *in silico* experiments on novel substituted series of analogues of quercetin and kaempferol to predict their biological activity.

MATERIALS AND METHODS:

Databases and Software (Computational Data): The flavonoids that were utilized for the study were quercetin and kaempferol. New substituted series of analogues of both flavonoids were designed using Maestro modeling suite of schrödinger software (https://www.schrodinger.com/maestro) [21]. Further QSAR analysis was used to calculate *in silico* biological activity of these new analogues which may have potential antipsoriatic activity. For this study, VLIFEMDS - QSARPro (www.vlifesciences.com) [24] version 3.5 was used as it consists of exhaustive regression analysis tools and facilities for prediction of biological activity. The configuration used for analysis was Lenovo computer with Intel core duo processor. The system comes with powerful pack of facilities for quantitative structure activity relationship analysis, statistical modeling, activity / property prediction and visualization [24 - 26] .

Biological Activity: Biological activity is used as dependent variable, for correlating the data linear to the free-energy change with other 2D descriptors like XLogP, hydrogen bond donors, hydrogen bond acceptors, *etc* [35]. For the development of quercetin and kaempferol QSAR models IC_{50} values in μM (*in vitro* biological activity in terms of half maximal inhibitory concentration) were taken from the PubChem database to predict biological activity of new analogues presented in **Annexure 1**.

Experimentally reported IC_{50} values (half maximal inhibitory concentration) were converted to pIC_{50} scale (−log IC_{50}) to narrow down the range. Thus, a higher value of pIC_{50} exhibits a more potent compound. These values were then manually incorporated in VLIFEMDS-QSARPro [31].

ANNEXURE 1: SPECIFICATION OF TRAINING SET DATA FOR 2D- QSAR

	Quercetin Training Set			Kaempferol Training Set		
Sr. no.	**Accession id: Pubchem Database**	**IC_{50} (μM)**	**pIC_{50} (μM)**	**Accession id: Pubchem Database**	**IC_{50} (μM)**	**pIC_{50} (μM)**
1	CID:118733751	8.2	5.09	CID:5280863	53.7	4.27
2	CID:118730331	91.2	4.04	CID:118733612	43.6	4.36
3	CID:71653621	18	4.74	CID:11644907	6.79	5.17
4	CID:71653184	9.15	5.04	CID:118713859	21.5	4.67
5	CID:71653480	8.4	5.07	CID:118708180	34	4.47
6	CID:71653183	9.5	5.02	CID:118708179	32	4.49
7	CID:71718277	8.6	5.07	CID:90676257	95	4.02
8	CID:71653763	2.4	5.62	CID:72205594	100	4
9	CID:71653481	0.48	6.32	CID:5281670	50	4.3
10	CID:71653330	0.39	6.41	CID:5281616	44	4.36
11	CID:71653623	0.68	6.17	CID:5281605	50	4.3
12	CID:71653622	9.2	5.04	CID:5280961	15.88	4.8

13	CID:71653327	0.24	6.62	CID:5280378	2.17	5.66
14	CID:71653329	0.45	6.35	CID:5280373	1	6
15	CID:71653181	9.6	5.02	CID:5280343	30.9	4.52
16	CID:71653479	0.8	6.1	CID:439246	100	4
17	CID:71653328	0.22	6.66	CID:11623068	3.8	5.43
18	CID:71653040	0.8	6.1	CID:14077266	29.4	4.54
19	CID:71653482	0.7	6.15	CID:31703	0.33	6.49
20	CID:71653478	0.38	6.42	CID:44446907	49.8	4.3
21	CID:71653182	8.2	5.09	CID:5280551	49.3	4.31
22	CID:66573474	3.58	5.45	CID:442811	7.3	5.14
23	CID:71718882	9.24	5.03	CID:44446856	29.8	4.52
24	CID:71653331	0.4	6.4	CID:25022738	5.9	5.23
25	CID:71653181	8.75	5.06	CID:73067	11.3	4.95
26	CID:71653474	4.56	5.34	CID:177032	49	4.31
27	CID:5311	0.71	6.15	CID:44446830	25.9	4.59
28	CID:95168	12.32	4.91	CID:44446828	27.8	4.55
29	CID:4871	3.95	5.4	CID:44437740	44.5	4.35
30	CID:118733605	12.5	4.9	CID:5319688	12.3	4.91
31	CID:5281691	7.8	5.11	CID:5376979	7.4	5.13
32	CID:42638983	7.1	5.15	CID:3385	0.46	6.34
33	CID:42638982	7.3	5.14	CID:638278	21.8	4.66
34	CID:44188970	6.4	5.19	CID:44446857	47.5	4.32
35	CID:31703	6.04	5.22	CID:11623068	6.3	5.2
36	CID:5280443	10	5	CID:16293774	25.9	4.59
37	CID:5280343	10	5	CID:5922786	27.4	4.56
38	CID:5281607	10	5	CID:71713338	44.5	4.35
39	CID:5281616	10	5	CID:5713287	32.6	4.49
40	CID:5281654	10	5	CID:12581596	17.6	4.75
41	CID:736186	10	5	CID:5912178	13.5	4.87
42	CID:68071	10	5	CID:14068741	9.1	5.04
43	CID:597405	10	5	CID:42616	2.8	5.55
44	CID:118708179	32	4.49	CID:639465	2.4	5.62
45	CID:16044716	21	4.68	CID:14539951	10	5

Note : CID: pubchem compound identification

Variable method chosen for analysis for quercetin was simulated annealing which is the simulation of a physical process, 'annealing', which involves heating the system to a high temperature and then gradually cooling it to a preset temperature (*e.g.*, room temperature). During this process, the system samples possible configurations distributed according to the Boltzmann distribution so that at equilibrium, low energy states are the most populated [33]. Variable method chosen for kaempferol analogues was one of the systemic variable method *i.e.* forward - backward because simulated method was not able to predict acceptable model parameters for these analogues.

For QSAR analysis the substitution ratio of test and training sets considered for generation of QSAR models of quercetin and kaempferol were taken in a ratio of 1:3 therefore each dataset of 15 new designed analogues of quercetin and kaempferol were taken as test set (independent variables).

Dataset of 45 structures of already available similar compounds to quercetin and kaempferol were taken as training set (dependent variable) along with their biological activity IC_{50} values [41] from PubChem database [42].

The 2D descriptors like thermodynamic, spatial and electronic parameters were calculated which resulted in 95 descriptors for quercetin and 100 for kaempferol generated in data matrix. From variable selection methods simulated annealing was chosen and then coupled with the three statistical model building methods MLR, PCR and PLS to develop final QSAR models [28, 34]. The parameters like cross-correlation limit was set at 1.000000, number of variables in the final equation to be generated was 10. For the model building methods MLR, PCR and PLS, term selection criteria as r^2, f-test 'in,' at 4.000000 and 'out' at 3.990000. Variance cutoff was set at 0.0, scaling to auto scaling and number of random iterations to 100.

RESULTS:

2D QSAR Model Development and its Validation: *In silico* QSAR analysis using VLIFE-QSARPro software was carried out defining the dataset into (training: test set) where quercetin and kaempferol test set was of 15 structures and training set of 45 structures each. Chemical structures of both parent flavonoids are shown in **Fig. 1** quercetin and kaempferol:

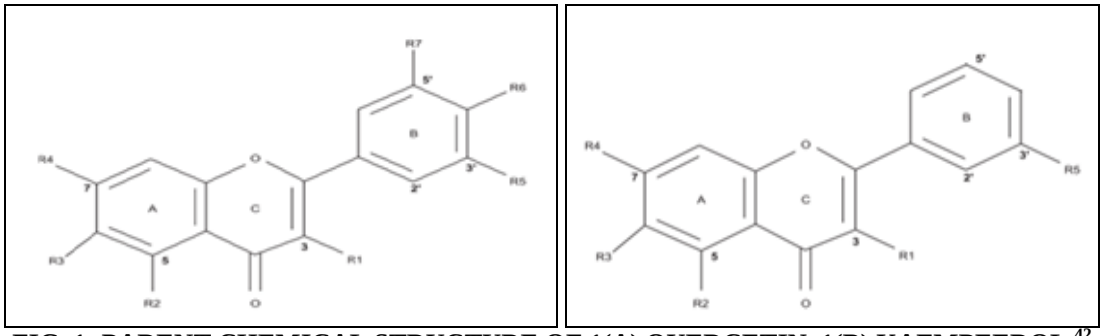

FIG. 1: PARENT CHEMICAL STRUCTURE OF 1(A) QUERCETIN, 1(B) KAEMPFEROL [42]

Annexure 1 shows training data set used for 2D QSAR analysis for quercetin and kaempferol new analogues that were retrieved from PubChem database with IC_{50} values converted to pIC_{50} values.

The details of the substituent groups created in parent structures positions of quercetin are presented as test set in **Table 1** whereas details of the substituent groups created in parent structure of kaempferol as test set are shown in **Table 2**.

TABLE 1: SPECIFICATION FOR TEST SET OF QUERCETIN ANALOGUES

	Positions and substitutions in parent flavonoid structure of quercetin as test set					
Quercetin Analogues Name	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**
Q11	CHO	$NHCH_3$	CHO	$NHCH_3$	-	-
Q15	CHO	NO_2	CHO	NO_2	-	-
Q19	CHO	CHO	CHO	CH_3	-	-
Q32	COC_2H_5	OH	COC_2H_5	OH	-	-
Q44	CN	CHO	CN	CHO	-	-
Q5	$NHCH_3$	$NHCH_3$	$COCH_3$	$COCH_3$	-	-
Q6	$NHCH_3$	$C=OCH_3$	$C=OCH_3$	$NHCH_3$	-	-
Q68	CHO	CHO	$COCH_3$	OC_2H_5	-	-
Q70	OC_2H_5	OC_2H_5	CN	CN	-	-
Q72	CHO	OC_2H_5	$COOC_2H_5$	$COCH_3$	-	-
Q76	-	OH	-	OCH_3	-	-
Q77	-	OH	-	-	-	-
Q78	-	OH	-	-	-	F
Q79	-	OH	-	F	F	-
Q8	OCH_3	CHO	CHO	CHO	-	-

Note: (-) indicates no substitution in that position.

Table 3 shows the best QSAR models predicted by VLIFE-QSARPro for substituted series of analogues of quercetin using simulated annealing variable selection method coupled with three model building methods like PLS, MLR and PCR. Similarly **Table 4** shows QSAR models developed for analogues of kaempferol using systemic variable selection method coupled with same above mentioned model building methods.

TABLE 2: SPECIFICATION FOR TEST SET OF KAEMPFEROL ANALOGUES

	Positions and substitutions in parent flavonoid structure of kaempferol as test set		
Kaempferol Analogues Name	**R1**	**R2**	**R3**
K3	$NHCH_3$	$C=O-CH_3$	$C=O-CH_3$
K14	C=O-O-C	C=O-O-C	OCC
K18	CN	CN	CHO
K19	CN	CHO	CHO

K31	C-O-C=O	$O=C-O-CH_2-CH_3$	$O=C-O-CH_3$
K38	OCH_3	$O=C-O-C_2H_5$	$O=C-O-C_2H_5$
K40	F	CHO	F
K43	CHO	$COOC_3H_7$	$COOC_2H_5$
K44	CHO	$COOC_3H_7$	$COOC_2H_5$
K48	F	$COCH_3$	$COCH_3$
K50	F	$COOC_2H_5$	$COOC_2H_5$
K51	$COOCH_3$	$COOC_2H_5$	$COOC_2H_5$
K56	F	$COOCH_3$	$COOC_2H_5$
K61	OCH_3	F	OCH_3

TABLE 3: 2D-QSAR MODELS PREDICTED FOR QUERCETIN ANALOGUES

Model number	Q1	Q2	Q3	Q4	Q4	Q6	Q7	Q8	Q9
Model building Method		**MLR**			**PLS**			**PCR**	
%	60	70	80	60	70	80	60	70	80
r2	0.7	0.9	0.7	0.9	0.79	0.7	0.5	0.7	0.6
q2	-3.1	-1.0	0.3	0.5	0.4	0.5	0.2	0.4	0.3

Note: % denotes the ratio of test set verses training set data.

TABLE 4: 2D - QSAR MODELS PREDICTED FOR KAEMPFEROL ANALOGUES

Model number	K1	K2	K3	K4	K5	K6	K7	K8	K9
Model building Method		**MLR**			**PLS**			**PCR**	
%	60	70	80	60	70	80	60	70	80
r2	0.7	0.6	0.5	0.7	0.5	0.4	0.5	0.4	0.5
q2	0.7	0.5	0.1	0.1	0.4	-0.1	0.4	-0.2	0.00

Note: % denotes the ratio of test set verses training set data

TABLE 5: OTHER STATISTICAL REGRESSION PARAMETERS OBTAINED FOR QUERCETIN ANALOGUES BEST MODEL (Q4) AND FOR KAEMPFEROL ANALOGUES BEST MODEL (K2)

Flavonoids	Quercetin	Kaempferol
Model building method	PLS	MLR
Model number	Q4	K2
%	60	70
N	26	31
DF	21	26
r^2	0.9021	0.687
q^2	0.5791	0.5676
F-test	48.4013	14.2654
r^2_se	0.2286	0.3823
q^2_se	0.4741	0.4986
Pred_ r^2	0.1074	0.0048
Pred_r^2se	0.5856	0.4819
$Z_{score\_ran\_r2}$	4.7648	7.52232
$Z_{score\_ran\_q2}$	2.24988	1.33145
Best_ran_r^2	0.67502	0.40784
Best_ran_q^2	0.17430	0.24601

Key : % = ratio of test set verses training set data, MLR = multiple linear regression, PLS = partial least squares, N = number of molecules of training set, Df = degree of freedom, r^2 = coefficient of determination, q^2 = cross-validated r ^{2}, pred-r^2 = r^2 for external test set, Z score = the Z score calculated by q^2 in the randomization test, best_ran_q^2 = the highest q^2 value in the randomization test and a_ran_q^2 = the statistical significance parameter obtained by the randomization test.

From the data obtained and shown in the above 2 tables, model Q4 and K2 were selected as promising models with best cross validated squared correlation coefficient $q^2 > 0.3$ for training set and $r^2 > 0.6$ for test set., which show accuracy of the statistical calculation. All other statistical regression expressions parameters were obtained using simulated annealing variable selection method in combination with model building method PLS for the model Q4 of Quercetin analogues. Similarly parameters were retrieved for K2 model of kaempferol analogues using systemic variable selection method coupled with MLR. These results are shown in **Table 5.** The Q4 and K2 models fulfill the selection criteria such as correlation coefficient $r^2 > 0.6$ for anti-

inflammatory activity with low standard error of squared correlation coefficient r^2_se < 0.3 show the relative good fitness of the model and F value > 11 times than tabulated F value show the 99% statistical significance of the regression model. These models fulfil all validation criteria with low standard error of cross validated squared correlation coefficient q^2_se < 0.3 and standard error of pred_r^2se < 0.1. The randomization test suggests that the developed model have a probability of less than 1 percent that the model was generated by chance [43, 44].

Quercetin: Model Q4: It gave a correlation coefficient r^2 of 0.9021, significant cross validated correlation coefficient q^2 of 0.5791, F test of 48.4013 and degree of freedom [21]. The model is validated by best_ran_r^2 = 0.67502, best_ran_q^2 = 0.17430, Z score$_{_ran_r2}$ = 4.7648 and Z $_{score\_ran\_q2}$ = 2.24988. Significance of model is shown by equations developed from analysis. Statistical data has been depicted in **Table 5**.

Equation for model Q4 IC_{50} = + 0.1421 XlogP- 0.0087 5 Path Count - 0.1223 SssO count - 0.0030 2 Path Count + 0.0165 0 Path Count - 1.3120 SsBr count- 1.9669 Sulfurs Count + 0.0797 SdOE-index + 0.1412 SdsCH count - 0.0812 chiV3 + 4.3399-(v)

Kaempferol: Model K2: The model K2 gave a correlation coefficient r^2 of 0.687 significant cross validated correlation coefficient q^2 of 0.5676, F test of 14.2654 and degree of freedom [26]. The model is validated by best_ran_r^2 = 0.40784, best_ran_q^2 = 0.24601, $Z_{score\_ran\_r2}$= 7.52232 and $Z_{score\_ran\_q2}$=-1.33145. Statistical data is shown in **Table 5.**

TABLE 6: PREDICTED BIOLOGICAL ACTIVITIES FOR QUERCETIN AND KAEMPFEROL ANALOGUES

Model	Q4		K2	
	Analogues	Predicted IC_{50} (µM)	Analogues	Predicted IC_{50} (µM)
1	Q11	6.962	K14	4.096
2	Q15	8.694	K18	4.497
3	Q19	8.049	K19	4.498
4	Q32	6.964	K3	4.438
5	Q44	6.929	K31	3.303
6	Q5	6.752	K38	3.765
7	Q6	6.754	K40	4.138
8	Q68	7.846	K43	3.612
9	Q70	4.839	K44	3.612
10	Q72	7.734	K48	4.029
11	Q76	5.12	K50	3.475
12	Q77	5.293	K51	3.303
13	Q78	5.276	K56	3.568
14	Q79	5.261	K61	4.327
15	Q8	7.865	K67	4.375

Note: Q: quercetin analogues, K: kaempferol analogues; Predicted biological activities (IC_{50}) of analogues in model quercetin (Q4) and kaempferol (K2).

Table 6 shows predicted biological activities of new analogues of Quercetin in model **Q4** and Kaempferol analogues in model K2.

Equation for Model K2 IC_{50} = - 0.2611 XlogP+ 0.3320 SdssCE-index - 0.4438 SsssCHE-index - 0.1215SaasCcount + 6.3433 ---------(vi)

The above two equations (v, vi) have led to the development of statistically significant QSAR models of quercetin and kaempferol analogues. In addition, this 2D QSAR study allowed investigating the influence of very simple and easy to compute descriptors in determining biological activities, which could shed light on the key factors that may aid in design of novel potent molecules. All the parameters along with their importance which may potentially contribute to the specific antipsoriatic inhibitory activity in the generated models, are discussed below. The fitness plot of observed *vs.* predicted activity of trained and test set data of analogues of quercetin and kaempferol is shown in **Fig. 2A** plot of quercetin model Q4 **Fig. 2B** plot of kaempferol model K2 . Actual *vs.* Predicted activities for training and test set data for quercetin predicted by PLS model building method is shown in **Fig. 3A** Similarly, for kaempferol analogues activities are predicted by MLR model building method as shown in **Fig. 3B**.

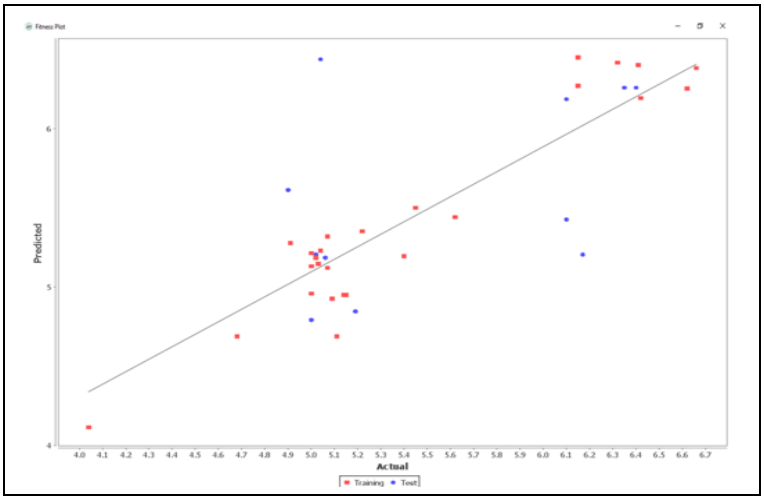

FIG. 2A: FITNESS PLOT OF QUERCETIN MODEL Q4

Key: The training set is represented by red dots and test set by blue dots

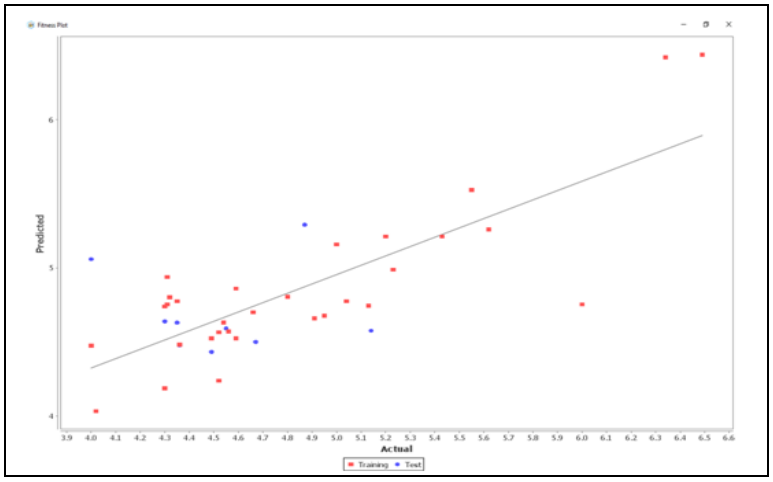

FIG. 2B: FITNESS PLOT OF KAEMPFEROL MODEL K2

Key: The training set is represented by red dots and test set by blue dots

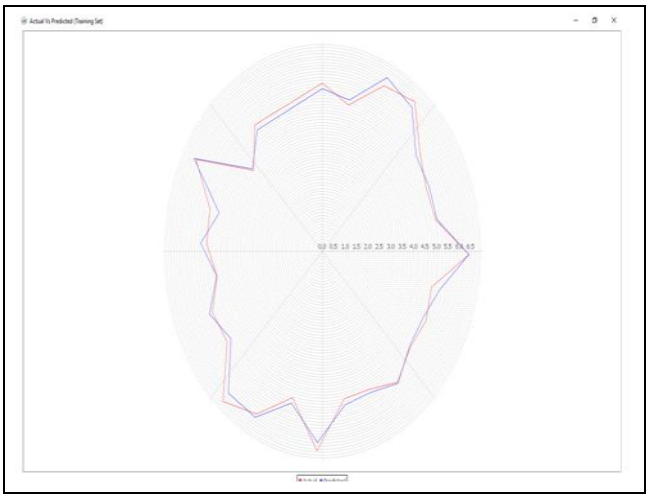

FIG. 3A: PLOT OF QUERCETIN MODEL Q4

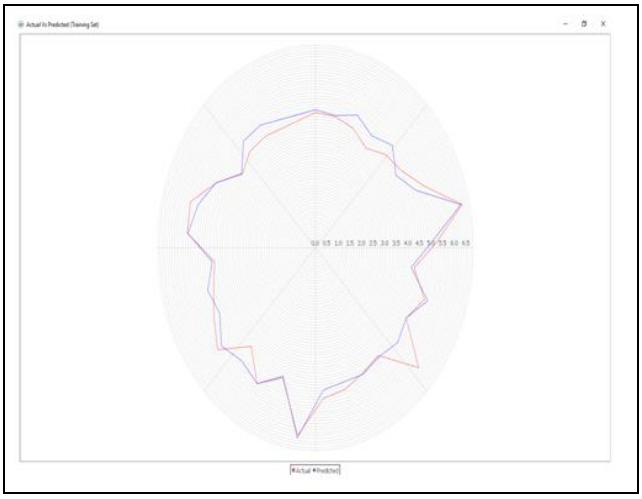

FIG. 3B: PLOT OF KAEMPFEROL MODEL K2

Key: Training set- Red dots and Test Set- Blue dots.

Contributing Parameters: In generated models of quercetin and kaempferol the important parameters which contributed to the specific biological activity or pharmacological actions with percentage contribution of each descriptor in developed models explaining variation in the biological activity are shown in **Fig. 4(A)** and **4(B)**.

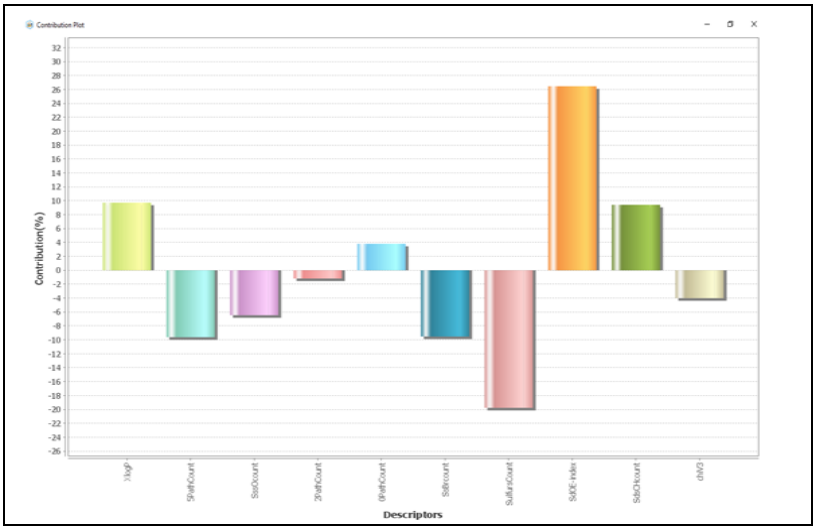

FIG. 4A: PERCENTAGE CONTRIBUTION PLOT OF EACH DESCRIPTOR IN DEVELOPED MODEL EXPLAINING VARIATION IN THE BIOLOGICAL ACTIVITY OF QUERCETIN MODEL Q4

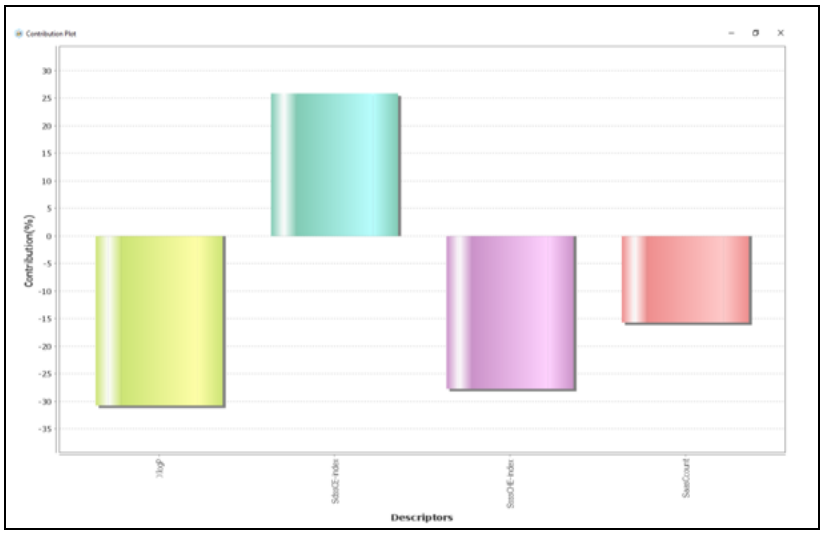

FIG. 4B: PERCENTAGE CONTRIBUTION PLOT OF EACH DESCRIPTOR IN DEVELOPED MODEL EXPLAINING VARIATION IN THE BIOLOGICAL ACTIVITY OF KAEMPFEROL MODEL K2

Following are the noteworthy observations from the contribution plot **Fig. 4A** for quercetin analogues:

1. XlogP = This descriptor signifies ratio of solute concentration in octanol and water and generally termed as Octanol Water partition Coefficient. This is atom based evaluation of logP contributed positively for +10 % towards the activity of structures.

2. 5 Path Count = This descriptor signifies total number of fragments of fifth order (five bond path) in a compound contributed negatively for -10 % towards the activity of structures.

3. SssO count = This descriptor defines the total number of oxygen connected with two single bonds contributed negatively for -7 % towards the activity of structures.

4. 2 Path Count = This descriptor signifies total number of fragments of second order (two bond path) in a compound contributed negatively for -1 % towards the activity of structures.

5. 0 Path Count = This descriptor signifies total number of fragments of zero order (atoms) in a compound contributed positively for +3 % towards the activity of structures.

6. SsBr count = This descriptor defines the total number of bromine atom connected with one single bond contributed negatively for -10 % towards the activity of structures.

7. Sulfurs Count = This descriptor signifies number of sulphur atoms in a compound contributed negatively for -20 % towards the activity of structures.

8. SdOE-index = Electrotopological state indices for number of oxygen atom connected with one double bond contributed positively for +26 % towards the activity of structures.

9. SdsCH count = This descriptor defines the total number of –CH group connected with one double and one single bond contributed positively for +9 % towards the activity of structures.

10. chiV3 = This descriptor signifies atomic valence connectivity index (order 3) contributed negatively for -4 % towards the activity of structures.

Similarly, following are the noteworthy observations from the contribution plot **Fig. 4B** for kaempferol analogues:

1. XlogP = This descriptor signifies ratio of solute concentration in octanol and water and generally termed as octanol water partition coefficient. This is atom based evaluation of logP contributed negatively for -30 % towards the activity of structures.

2. SdssCE-index = Electrotopological state indices for number of carbon atom connected with one double and two single bonds contributed positively for +25 % towards the activity of structures.

3. SsssCHE-index = Electrotopological state indices for number of –CH group connected with three single bonds contributed positively for -27 % towards the activity of structures.

4. SaasC count = This descriptor defines the total number of carbon connected with one single bond along with two aromatic bonds contributed positively for -15 % towards the activity of structures.

5. The predicted biological activity IC_{50} of the test set molecules of quercetin and kaempferol are already presented in **Table 6** as best predicted model values. These values were predicted as output file from VLIFE-QSARPro software.

DISCUSSION: The 2D QSAR analysis was performed using VLIFE-QSARPro software where 15 each new substituted series of designed quercetin and kaempferol analogues were taken as test sets (calcineurin protein inhibitors) and 45 similar compounds for each of these flavonoids from Pubchem database were used as training sets. QSAR analysis revealed useful information regarding the structural features of novel analogues by calculating the descriptor like (logp, molecular weight, hydrogen bond donor and acceptor) and predicting which descriptors are favoring the structures.

Firstly, we tried to develop models with systemic variable selection method *i.e.* forward- backward for both flavonoid analogues in combination with model building methods like MLR, PLS and PCR but the attempt was not successful for quercetin analogues. The resulted quercetin QSAR models generated were not validated successfully. (data not shown). Therefore simulated annealing variable selection method was the criteria used for QSAR analysis for quercetin analogues in combination with model building methods like MLR, PLS and PCR which gave validated QSAR models. In this analysis total 9 QSAR models were obtained for quercetin and kaempferol. The PLS method for quercetin has shown promising results with model Q4. Whereas for kaempferol analogues model K2 has significant results from MLR method coupled with systemic variable method.

In above QSAR models, r^2 is a correlation coefficient that has been multiplied by 100 to give explained variance in biological activity where r^2 was > 0.6. Predictive ability of generated QSAR models was evaluated by q^2 employing LOO method. F-test value reflects ratio of variance explained by models and variance due to error in regression. In these models high F-test value indicates that model is statistically significant. Cross validated q^2 of the models were $q^2 > 0.3$ indicates good internal prediction power of the model. Another parameter for prediction of test set analogues structures is high pred_$r^2 > 0.4$, which shows good external predictive power of the model [45].

The best model of quercetin Q4 model revealed the presence of SdOE-index (oxygen atoms), SdsCH count (CH atoms) that favor the activity in analogues of quercetin (equation 5). Mahesh *et al.*, (2011) has reported QSAR studies on fluoroquinolone to inhibit DNA gyrase, reveals that out of all three optimized models, MLR method has giving significant results. The estate contribution, chi, path cluster and alignment independent descriptors were major contributors [30].

Sharma (2015) has employed similar QSAR analysis to study the quantitative effects of the molecular structure of the benzimidazoles on their activity as inhibitors of IgE response. In this model special emphasis was given to the contribution of electrotopological indices in predicting biological activity of 2- phenyl-benzimidazole derivatives and they were found to improve the QSAR model and make it more precisely predictive [35].

Whereas in our case, the best model of kaempferol K2 gave very significant results and revealed the presence of SdssCE-index (carbon atom) favoring the activity of analogues (equation 6). Doreswamy *et al.*, (2014) has conducted similar kind of studies with a series of Sulfathiazoles derivatives for Mycobacterium tuberculosis (H37Rv) inhibitors, and some useful predictive molecular models were obtained where Chi2 and SdsN count contributes positively towards the sulfathiazoles derivatives. This suggests that by change in number of chi2 and SdsN count will be helpful for designing of more potent (H37Rv) inhibitors [27].

B Bertosa *et* al., (2012) have conducted 2D-QSAR studies of substituted pyrazolone derivatives as anti-inflammatory agents and shown that their model fulfils the selection criteria's such as correlation coefficient r^2 > 0.8 for anti-inflammatory activity with low standard error of squared correlation coefficient r^2 _se <0.3 show the relative good fitness of the model and F value > 11 times than tabulated F value show the 99% statistical significance of the regression model. Two descriptors as chi2 and SdsN count contribute positively to models [44, 45].

CONCLUSION: The novel substituted series of analogues of quercetin and kaempferol were subjected to QSAR analysis and the best model was Q4 built using PLS method showed significant predictive power and reliability as compared to other two methods. Similarly, from kaempferol analogues, model K2 predicted significant results with MLR method coupled with systemic variable method. It is anticipated that the present study may prove to be helpful in development and optimization for newly designed antipsoriatic agents. Hence the models proposed in this work are expected to be useful and can be employed to design new analogues of flavonoids with specific antipsoriasis inhibitory activity.

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