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Review on Qsar Studies of Flavonoids

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ABSTRACT

The primary component of flavonoids is a benzopyrone ring with phenolic or polyphenolic groups positioned in various locations. The most frequent places where they may be found are in fruits, herbs, stems, grains, nuts, vegetables, flowers, and seeds. These various plant parts' medicinal worth and biological activity are due to the bioactive phytochemical elements that are found in them. Over 10,000 flavonoid chemicals have so far been isolated and figured out. The majority of flavonoids are used therapeutically with great success. These are produced in nature through the phenylpropanoid pathway, and the bioactivity depends on how well they are absorbed and bioavailable. The introduction of computer-aided drug design (CADD) methodology is crucial to accelerating the cumbersome process of traditional drug discovery. Two of the useful CADD techniques for drug design and activity prediction are quantitative structure-activity relationships (QSAR) and molecular docking. It is typical for QSAR to examine a large number of compounds, producing models that can forecast the potency or activity of novel or even unsynthesized molecules. The exhaustive literature reviews revealed that QSAR studies of flavonoids resulted in the reporting of flavonoids as antibacterial agents, antioxidants, Differential inhibition of aldose reductase and p56(lck) protein tyrosine kinase, activation of voltage-gated calcium channels in osteogenesis, inhibitory effect of flavonoids on OCT2-mediated uptake of4–4-dimethyl amino styryl-N-methyl pyridinium (ASP^+), influenza H1N1 virus neuraminidase inhibitors, aromatase inhibitory properties of flavonoids as breast cancer therapeutics, CYP1A2 inhibitor flavonoids using 2D and 3D descriptors, flavonoid analogs as in vivo anticancer BCRP inhibition bio-activity, Natural α-Glucosidase Inhibitors, therapeutic drug for Alzheimer's disease, natural estrogen-like activity, PDE5A inhibitors, vascular relaxant activity in coronary heart diseases.

I. INTRODUCTION

The QSAR/QSPR methods are predicated on the idea that a particular chemical compound's activity or propriety—such as a medicine binding to DNA or poisonous effect—relates to its structure through a specific mathematical formula. The element or biological process connected to a chemical compound's molecular structure. After that, this relationship may be utilized in the interpretation, evaluation, and prediction of novel compounds with desired actions or qualities that reduce and rationalize the synthesis process's time, effort, and cost development of new products.[1]

QSAR techniques are now used more and more in toxicology and ecological sciences. There have been several efforts to forecast utilizing QSAR and determine the chemicals' mutagenicity. Hansch and his team, for instance, investigated aromatic and hetero-aromatic amines to test for mutagenicity Test. The research revealed that hydrophobicity is the primary factor affecting the relative mutagenicity, in addition to steric and electronic characteristics are only marginally significant whereas the aromatic ring system's size has a modest or has no impact on mutagenicity. the same team expanded upon nitro compounds to produce a bilinear formula. The carcinogenicity and mutagenicity of several amines were also studied using QSAR. The link between mutagenic and carcinogenic potencies was found to be considerable. Quinolines showed a correlation between log P and electronic characteristics and mutagenic potential. It was proposed that the quinoline's 2 - position is the location of metabolic activation. It was discovered that lipophilicity affected the bio-concentration of pesticides in the food chain. While more polar phosphates are regarded as reasonably benign, DDT and other chlorinated hydrocarbons that are lipophilic are commonly involved in environmental toxicity.[2]

Plants contain naturally occurring substances called flavonoids. Their phenolic

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structures might vary. According to their stereochemistry, flavonoids have a 15-carbon skeleton made up of two benzene rings that are connected by a heterocyclic pyrane ring. Numerous classifications have been established for flavonoids. Flavonoids are produced through the phenylpropanoid pathway. Consuming foods high in flavonoids, which are polyphenolic phytochemicals found in fruits, nuts, and vegetables and have a wide range of structural variations, has been linked to a number of positive health effects, such as a longer life expectancy, fewer cardiovascular issues, and a lower incidence of metabolic illnesses. Individual flavonoids have been the subject of preclinical research that shows they have anti-inflammatory, anti-cancer, and immune-boosting properties. A more mechanistic, precision medicine approach will be necessary for the effective development of flavonoids for therapeutic applications.

- Improvements in general and tissue-specific administration techniques to increase flavonoid bioavailability.
- It is important to identify and use response-specific mechanisms for inflammatory and age-related disorders in chemotherapy and cancer prevention.
- Structure-activity investigations must be carried out to determine the most active (optimal) flavonoid once mechanism-based intracellular targets necessary for certain flavonoid-mediating responses have been identified.
- The use of mixtures of active flavonoids is necessary to optimize the chemopreventive and chemotherapeutic uses of flavonoids.

Once the aforementioned is done, it will be much easier to translate flavonoids' varied and incredibly promising disease-preventive effects in various models into therapeutic applications that can be utilized both alone and in medication combinations to treat non-cancer and cancer endpoints.[3, 4]

The major causes of flavonoids' pharmacological effects are their antioxidant activity and the inhibition of certain enzymes. Despite the wealth of available data, the structural prerequisites and processes behind these impacts remain poorly understood. The current state of understanding about quantitative structure-activity relationships (QSARs) and structure-activity relationships (SARs) of flavonoids' antioxidant activity is presented in this study. Tools like SAR and QSAR might be helpful in identifying the kind of flavonoid antioxidant activity. Additionally, they could support the development of innovative, effective flavonoids that have the potential to be employed as medicines.[5]

II. LITERATURE REVIEW

Yajing Fang et al (2015) evaluated the 3D-QSAR and docking studies of flavonoids as potent Escherichia coli inhibitors. The CoMFA and CoMSIA were developed by using the pIC_{50} values of flavonoids. The cross-validated coefficient (q^2) values for CoMFA (0.743) and for CoMSIA (0.708) were achieved, illustrating high predictive capabilities. Selected descriptors for the CoMFA model were ClogP (logarithm of the octanol/ water partition coefficient), steric and electrostatic fields, while, ClogP, electrostatic, and hydrogen bond donor fields were used for the CoMSIA model. Molecular docking results confirmed that half of the tested flavonoids inhibited DNA gyrase B (GyrB) by interacting with ATP pocket in the same orientation. Polymethoxyl flavones, flavonoid glycosides, and isoflavonoids changed their orientation, resulting in a decrease in inhibitory activity. Also, docking results showed that 3-hydroxyl, 5-hydroxyl, 7-hydroxyl, and 4-carbonyl groups were found to be crucial active substituents of flavonoids by interacting with key residues of GyrB, which were in agreement with the QSAR study results. These results provide valuable information for the structure requirements of flavonoids as antibacterial agents.[6]

Bakhtiyor F. Rasulev et al (2005) investigated the Quantitative Structure-Activity Relationship (QSAR) Study of the Antioxidant Activity of Flavonoids. The GA-MLRA analysis shows that the position of the OH groups, the magnitude of dipole moment, and the shape of the molecule play an important role in the inhibition of lipid peroxidation by flavonoids. The significant QSAR models were obtained with r value of 0.935 and 0.933 for basic models. The q^2 (cross-validation r^2) values and scrambling/randomization experiments also confirm the statistical significance of our models.[7]

A Stefanic-Petek et al (2002) evaluated the QSAR of flavonoids for Differential inhibition of aldose reductase and p56(lck) protein tyrosine kinase. It was revealed that Kinetic analyses of the PTK inhibition indicate that flavonoids are competitive inhibitors with respect to the nucleotide ATP. A thorough investigation of the available experimental database by using both classical and quantum chemical descriptors has

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been performed in order to develop quantitative structure-activity relationships for these enzyme systems. Relevance of the descriptors to binding properties of both enzyme receptors active sites is proposed and the obtained results demonstrate in detail which specific electronic as well as the hydrophobic and steric properties of the substituents play a significant role in their differential binding.[8]

Chan et al (2020) reported the Predictive QSAR model of flavonoids to activate voltage-gated calcium channels in osteogenesis. The model has shown these flavonoids have high activating effects on the Ca channel for osteogenesis. In addition, scutellarein was ranked the highest among the screened flavonoids, and other lower-ranked compounds, such as daidzein, quercetin, genistein, and naringin, have shown the same descending order as previous animal studies. This predictive modeling study has confirmed and validated the biochemical activity of the flavonoids in the osteoblastic Ca activation.[9]

Yajuan Bi et al (2022) investigated the inhibitory effect of flavonoids on OCT2-mediated uptake of4–4-dimethylaminostyryl-N-methylpyridinium (ASP^+). Among them, scullcapflavone II demonstrated the strongest inhibitory effect on OCT2-mediated uptake of ASP^+ in a competitive manner. The 3D-QSAR analyses of flavonoid OCT2 inhibitors were performed using both CoMFA and CoMSIA models. The data revealed that bulky substituents at the C-3 and C-4 positions of ring C and the C-7 position of ring A could prevent the interactions of flavonoids with OCT2. The hydrophilic and negatively charged substituent on ring A was favorable for the interactions of flavonoids with OCT2. Consequently, baicalin with a uronic acid substituent on ring A exhibited a stronger inhibition than baicalein; quercetin-3-O-galactoside was a stronger inhibitor of OCT2 than rhamnetin 3-galactoside. Thus, the determinant of renal excretion of various endogenous and exogenous organic cations can be monitored by this model.[10]

Andrew G. Mercader et al (2010) evaluated the QSAR study of flavonoids and biflavonoids as influenza H1N1 virus neuraminidase inhibitors. The best linear model constructed from 20 molecular structures incorporated four molecular descriptors, selected from more than a thousand geometrical, topological, quantum-mechanical, and electronic types of descriptors. The obtained model suggests that the activity depends on the electric charges, masses, and polarizabilities of the atoms present in the molecule as well as its conformation. The model showed good predictive ability established by the theoretical and external test set validations.[11]

Pablo R. Duchowicz et al (2008) investigated the QSAR modeling of the interaction of flavonoids with GABA(A) receptors. The best linear model established on 78 molecular structures incorporated four molecular descriptors, selected from more than a thousand geometrical, topological, quantum-mechanical, and electronic types of descriptors and calculated by Dragon software. An application of this QSAR equation was performed by estimating the binding affinities for some newly synthesized flavonoids displaying 2-,7-substitutions in the benzopyrane backbone which still do not have experimentally measured potencies.[12]

Chanin Nantasenamat et al (2014) reported QSAR modeling of aromatase inhibition by flavonoids using machine learning approaches. The quantitative structure-activity relationship (QSAR) and classification structure-activity relationship (CSAR) studies were performed on a non-redundant set of 63 flavonoids using multiple linear regression, artificial neural network, support vector machine, and decision tree approaches. The descriptors used were molecular size, flexibility, polarity, solubility, charge, and electronic properties to describe the unique physicochemical properties of the investigated flavonoids. The QSAR models provided good predictive performance as observed from their statistical parameters with Q values in the range of 0.8014 and 0.9870 for the cross-validation set and Q values in the range of 0.8966 and 0.9943 for the external test set. Furthermore, CSAR models developed with the J48 algorithm are able to accurately classify flavonoids as active and inactive as observed from the percentage of correctly classified instances in the range of 84.6 % and 100 %. The study therefore represents the QSAR study of aromatase inhibition on flavonoids which may provide an important insight into the origins of aromatase inhibitory properties of flavonoids as breast cancer therapeutics.[13]

Kunal Roy et al (2008) reportedComparative QSAR studies of CYP1A2 inhibitor flavonoids using 2D and 3D descriptors. The best model (genetic partial least squares model using two-dimensional descriptors) was selected based on the highest external predictive R (2) (R (2) (pred)) value (0.840) and the lowest root mean square error of prediction value (0.351). The

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developed QSAR equations suggest the importance of the double bond present at 2 and 3 positions and the requirement of the absence of hydroxyl substituent or glycosidic linkage at 3 positions of the 1,4-benzopyrone nucleus. Furthermore, the phenyl ring present at 2 positions of the 1,4-benzopyrone ring should not be substituted with the hydroxyl group. Moreover, hydroxyl groups present at the 5 and 7 positions of the benzopyran nucleus should not be glycosylated for good cytochrome P450 1A2 enzyme inhibitory activity.[14]

Carla Araya-Cloutier et al. (2018) investigated the QSAR-based molecular signatures of prenylated (iso)flavonoids underlying antimicrobial potency against and membrane-disruption in Gram-positive and Gram-negative bacteria such as Listeria monocytogenes and Escherichiacoli (the latter in combination with an efflux pump inhibitor). Minimum inhibitory concentrations of the most active compounds ranged between 6.3–15.0µg/ml. The QSAR analysis was performed and linear regression models were proposed with R^2 between 0.77–0.80, average R^2 m between 0.70–0.75, Q^2_{LOO} between 0.66–0.69, and a relatively low number of descriptors. A 3D pharmacophore model explaining the effect of the prenyl position on the activity of compounds was developed for each bacterium. These models predicted active compounds with an accuracy of 71–88%. The mode of action, of selected prenylated (iso)flavonoids with low relative hydrophobic surface area caused remarkable membrane permeabilization, whereas those with higher relative hydrophobic surface area did not.[15]

Jun-Zhen Qian et al (2015) evaluated the QSAR study of flavonoid-metal complexes scavenging $O_2^{\cdot-}$. Using the density functional theory technique, the structures of 31 flavonoid-metal complexes were optimized based on their antioxidant capabilities scavenging O_2, and then 21 quantum chemistry descriptors such as dipole, charge, and energy were estimated. Then, using stepwise linear regression, a number of quantum chemistry descriptors crucial to the IC_{50} of the antioxidant activities of flavonoid-metal complexes for scavenging O_2. With the help of the main component analysis, six additional variables were discovered. Finally, using an artificial neural network, QSAR models were constructed employing the six new variables as independent variables, the IC_{50} as the dependent variable, and crucial quantum chemistry descriptors. Utilizing experimental data from references, the model was verified. These findings demonstrate the validity and predictability of the model used in this research.[16]

Shailja Sachan et al (2014) reported a QSAR study of flavonoidanalogs as in vivo anticancer BCRP inhibition bio-activity. A multiple linear regression (MLR) model using the stepwise method based on 24 molecules has been developed for the prediction of the EC_{50} of some anticancer drugs using these quantum chemical descriptors, the most important class in modeling these series of compounds followed by constitutional, topological and physicochemical descriptors derived from e-dragon. The accuracy of the proposed MLR model was illustrated using the following evaluation techniques: cross-validation, and Y-randomization. The results obtained showed the excellent prediction ability and stability of the proposed model in the prediction of anticancer BCRP inhibition bio-activity of flavonoidanalogs found satisfactory and could be used for designing a similar group of anticancer drugs.The present study affirms positions 8, and 14 respecting the pattern molecule as the most suitable ones for producing an increase in BCRP inhibition activity. The Position No. 7 may present adverse drug interactions.[17]

Liang Zhao et al. (2022) reported the Construction of an MLR-QSAR Model Based on Dietary Flavonoids and Screening of Natural α-Glucosidase Inhibitors. The molecular fingerprint similarity clustering analysis was performed on the target molecules. The MLR-QSAR models of dietary flavonoids (2D descriptors and 3D descriptors optimized), with R2 of 0.927 and 0.934, respectively, were constructed using genetic algorithms. Finally, the MolNatSim tool based on the COCONUT database was used to match the similarity of each flavonoid in this study and to sequentially perform molecular enrichment, similarity screening, and QSAR prediction. After the screening, five kinds of natural product molecules (2-(3,5-dihydroxy phenyl)-5,7-dihydroxy-4H-chromen-4-one, norartocarpetin, 2-(2,5-dihydroxy phenyl)-5,7-dihydroxy-4H-chromen-4-one, 2-(3,4-dihydroxy phenyl)-5-hydroxy-4Hchromen-4-one, and morelosin) were finally obtained. Their IC_{50}pre-values were 8.977, 31.949, 78.566, 87.87, and 94.136 µM, respectively. Pharmacokinetic predictions evaluated the properties of the new natural products, such as bioavailability and toxicity. Molecular docking analysis revealed the interaction of candidate novel natural flavonoid compounds with the amino acid residues of α-glucosidase.

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Molecular dynamics (MD) simulations and molecular mechanics/generalized Born surface area (MMGBSA) further validated the stability of these novel natural compounds bound to α-glucosidase. The present findings may provide new directions in the search for novel natural α-glucosidase inhibitors.[18]

M.R. Islam et al. (2013) evaluated the in silico QSAR analysis of quercetin revealing its potential as a therapeutic drug for Alzheimer's disease. The binding strength for quercetin in the active site of the enzyme was -8.8 kcal/mol, which was considerably higher than binding scores for some of the drugs such as donepezil (binding score -7.9 kcal/mol). Fifteen hydrogen bonds were predicted between quercetin and the enzyme whereas conventional drugs had fewer or even no hydrogen bonds. It implies that quercetin can act as a better inhibitor than conventional drugs. To find even better inhibitors, similar structures of quercetin were searched through the SIMCOMP database and a methylation in the 4-OH position of the molecule showed better binding affinity than parent quercetin. A quantitativestructure-activity relationship study indicated that O-4 methylation was specifically responsible for better affinity. This in silico study has conclusively predicted the superiority of the natural compound quercetin over conventional drugs as an AchE inhibitor and it sets the need for further in-vitro study of this compound in the future.[19]

Uma Devi Bommu et al. (2017) Investigated the therapeutic potential of quercetin analogs as effective anticancer drugs against the human epidermal growth factor receptor (EGFR), which is a reliable marker for regulating non-small-cell lung carcinoma (NSCLC). Here, the pharmacophore approach, molecular docking, and ligand-based virtual screening were developed as logical methods for identifying small analogs against the ligand-binding domain of the EGFR (PDB code: 1XKK). According to adverse effects, toxicogenomics, and pharmacokinetics, 10 candidates demonstrated credible outcomes with fewer side effects and higher target receptor efficiency.According to protein-ligand interaction profiles, the intricacy and stability of the receptor structure are supported by possible H-bonds, atomic contacts, salt bridges, and van der Waals interactions; as a result, they may make it more difficult to produce a single mutation that results in drug resistance. The lead scaffolds, which are thought to be flexible and experimentally proven compounds, are explained by in silico anticancer characteristics. The total findings suggested that established leads might be used as reference skeletons for fresh EGFR inhibitors aiming to treat NSCLC and other malignant conditions.[20]

Nicolas Alejandro Szewczuk et al. (2020) investigated the quantitative structure-activity relationships (QSAR) theory is applied to predict the cytochrome P450 3A4 inhibition constant by anthocyanin derivatives. Different freely available software calculated 102,260 non-conformational molecular descriptors. A training set of 12 compounds was used to calibrate the best univariable linear regression models, while a test set of 4 compounds was used to explore their predictive capability. The present results were compared with previously reported ones by using 3D-QSAR, thus demonstrating that the proposed topological QSAR models achieve acceptable statistical quality. The proposed model provides a prospective QSAR guide for the search for new anthocyanin derivatives possessing high or low predicted mutagenicity.[21]

Rastija, V. et al (2009) reported the QSAR study of lipid peroxidation inhibitory effect of catechins, anthocyanidins, and anthocyanins using molecular descriptors and physicochemical parameters derived from optimized three-dimensional (3D) structure, Six groups of 3D descriptors were used to generate QSAR models: geometrical, 3D molecule representation of structures based on electron diffraction (3D-MoRSE); Randic molecular profiles; geometry, topology and atom weights assembly (GETAWAY); radial distribution function (RDF); and weighted covariance matrices (WHIM) descriptors. The 3D molecular descriptors and physicochemical parameters were calculated by applying the online software Parameter Client and HyperChem 8.0. The primary selection of 3D molecular descriptors and physicochemical parameters was based on their ability to discriminate stereoisomers. The selection of predictor variables for multiple regression was performed by the best-subset and forward stepwise method. The best-developed QSAR models consisted of geometrical, RDF, and Randic molecular profile descriptors. Those descriptors could be used for the prediction of the biological activity of catechin stereoisomers and their derivates. The obtained models suggest that the inhibitory effect of studied compounds is related to the shape of the molecule and the three-dimensional distribution of atomic mass in the molecule.[22]

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Wanchai De-Eknamkulet al (2011) evaluated the QSAR study of natural estrogen-like isoflavonoids and diphenolics from Dalbergia parviflora and Belamcanda chinensis. A set of some 55 isolated isoflavonoids and diphenolics showed a wide range of estrogen activity as determined in breast cancer MCF-7 and T47D cell proliferation assays. This set of compounds was studied by means of computational techniques including QSAR and molecular modeling. It was found that the estrogenic potencies of the studied compounds depend mainly upon the presence/absence of hydroxyl groups attached to the 3' and 5' positions of the B ring of the isoflavone scaffold and the inter-atomic distance between the hydroxyl groups attached to the outer terminal positions 7 of A ring and 4' of B ring. In a QSAR model employing ligand-receptor interaction energy descriptors, the LigScore scoring function of Cerius (2) virtual screening module, which describes the receptor affinities of simultaneous binding to estrogenic receptors α and β (ER(α) and ER(β)), led to the best correlation between the observed estrogenic activities and computed descriptors.[23]

Vipin Kumar et al (2010) reported Pharmacophore modeling and 3D-QSAR studies on flavonoids as α -glucosidase inhibitors. Pharmacophore mapping studies were undertaken for a set of 29 flavonoids as α-glucosidase inhibitors. Four-point pharmacophores with two hydrogen bond acceptors, one hydrogen bond donor, and one aromatic ring as pharmacophoric features were developed. Amongst them, the pharmacophore hypothesis AADR1 yielded a statistically significant 3D-QSAR model with 0.903 as an R^2 value and was considered to be the best pharmacophore hypothesis. The developed pharmacophore model was externally validated by predicting the activity of test set molecules. The squared predictive correlation coefficient of 0.69 was observed between experimental and predicted activity values of test set molecules. The geometry and features of the pharmacophore were expected to be useful for the design of selective α-glucosidase inhibitors.[24]

Li et al. (2022) reported the Isolation, bioassay, and 3D-QSAR analysisof 8-isopentenyl flavonoids from Epimediumsagittatum maxim. leaves as PDE5A inhibitors. The cellular effects of the examined flavonoids served as confirmation of the findings. Icarin, 2-O-rhamnosylicaridide II, and Baohuoside I were identified as isolated compounds with significant activity (IC_{50}=8.275, 3.233, and 5.473 M, respectively). Then, 3D-QSAR investigations revealed that the inhibitory effects might be increased by substituting C8 with bulky steric groups like isopentenyl, C3 with positive charge groups, and C4' with a hydrogen bond acceptor substituent. In contrast, the efficacies tended to decline when C7 was replaced by large steric or hydrophilic groups. By activating PKG, compounds 1, 2, and 3 may lower cytoplasmic Ca^{2+} and raise cGMP levels in rat corpus cavernosum smooth muscle cells (CCSMCs).8-isopentenyl flavonoids may be the primary PFES pharmacodynamic agents used in therapy for

treatment ED and several of them significantly inhibited PDE5A1 to stimulate the cGMP/PKG/Ca^{2+} signaling pathway that was connected to the substituents at the critical sites like C8, C3, C4, and C7 in the characteristic compounds.[25]

Prajakta Dongare (2017) investigated the 3D QSAR studies of flavonoid analogs for vascular relaxant activity in coronary heart diseases. In this study, the 3D QSAR study was performed on a series of 17 flavonoid analogs using the k nearest neighbor Molecular Field Analysis (kNN-MFA) approach for both electrostatic and steric fields. There was Simulated Annealing (SA), 3D QSAR method used for the development of the model and tested successfully for internal (q2= 0.6262) and external (predictive r2= 0.4675) validation criteria. Thus, the 3D QSAR model showed that electrostatic effects dominantly determine the binding affinities for vascular relaxant activity.[26]

M. Hariono et al. (2021) investigated the Potential SARS-CoV-2 3CLpro inhibitors from chromene, flavonoid, and hydroxamic acid compounds based on FRET assay, docking, andpharmacophore studies. At 1000 g/mL, methanolic extracts, from the leaves of Averrhoa carambola and the aerial portion of Ageratum conyzoides, showed>50% inhibition.Interestingly, the hydroxamic acid molecule N-isobutyl-N-(4-methoxyphenylsulfonyl) glycyl hydroxamic acid (NNGH), which is one of the flavonoids, exhibits 69% inhibition at 100 M as well as apigenin, which exhibits 92% inhibition at 250 g/mL (925 M). The docking experiments showed that both drugs mostly interact with the GLU166 residue in the 3CLpro's hydrophobic pocket supporting the in vitro data. The results were further corroborated by pharmacophore mapping, which demonstrated that the in vitro activities of both compounds were caused by the pharmacophore properties of hydrogen bond acceptor (HBA), hydrogen bond

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donor (HBD), and hydrophobic interactions.According to a Gas Chromatography-Mass Spectrometry (GC-MS) investigation, the methanolic extract of the Ageratum conyzoides aerial portion contains chromene chemicals that have the potential to be this enzyme inhibitor candidate. All of these outcomes demonstrate their potential. SARS-CoV-2 drugs that work by inhibiting 3CLpro[27]

D. Bhowmik et al. (2021) reported the Evaluation of flavonoids as 2019-nCoV cell entry inhibitors through molecular docking and pharmacological analysis

III. CONCLUSION

Flavonoids are widespread in nature, mainly in green plants, and exert a protective effect against both UV light and microbial invasion by pathogens in plants. Flavonoids, which were first isolated from herbal plants and used as tranquilizers in folk medicine, have been shown to possess a selective and relatively mild affinity for the benzodiazepine binding site of γ-amino butyric acid type A receptors. This new family of natural products, along with various synthetic derivatives, has an extremely potent anxiolytic effect that is not associated with myorelaxant, amnestic, or sedative actions. Inhibition in the adult mammalian central nervous system (CNS) is mediated by GABA. The fast-inhibitory actions of GABA are mediated by GABAARs, which mediate both phasic and tonic inhibition in the brain.

QSAR of flavonoids for the inhibition of cAMP phosphodiesterase has been determined and new inhibitors of xanthine oxidase have also been developed using a rational design approach. A 3-dimensional quantitative structure–activity relationship (3D-QSAR) has been applied to explore the structural requisites of flavone derivatives. The methods and software used for 4D-QSAR model establishment and analysis (including descriptor calculation and selection, partial least-squares–PLS- analysis, and related software) have been described in our previous publication with MCET. Multiple complementary applications of the 4DQSAR paradigm may be a good way to extend our knowledge and understanding of the SARs of flavonoids using this „quality for quantity" argument. The fourth „dimension" of the 4D-QSAR paradigm is ensemble sampling of the spatial features of the members of the training set. This sampling process in turn enables the construction of optimized dynamic spatial 4D-QSAR.

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