Available online on 15.04.2022 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Research Article

ADME-Tox profile of Cuminaldehyde (4-Isopropylbenzaldehyde) from *Cuminum cyminum* seeds for potential biomedical applications

S. Ramya[1], T. Loganathan[2], M. Chandran[3], R. Priyanka[3], K. Kavipriya[4], Grace Lydial Pushpalatha G.[5], Aruna Devaraj[6], Abraham GC.[7], and R. Jayakumararaj[8]*

[1] *PG Department of Zoology, Yadava College (Men), Thiruppalai - 625014, Madurai, TamilNadu, India*
[2] *Department of Plant Biology & Plant Biotechnology, LN Government College (A), Ponneri, TN, India*
[3] *Department of Zoology, Thiruvalluvar University, Serkadu, Vellore-632 115, TamilNadu, India*
[4] *Department of Zoology, Arignar Anna Government Arts College (W), Walajapet-632 513, TN, India*
[5] *PG Department of Botany, Sri Meenakshi Government Arts College, Madurai-625002, TN, India*
[6] *Rajendra Herbal Research Training Centre, Tamaraikulam, Periyakulam, Theni District, TN, India*
[7] *PG & Research Department of Botany, The American College, Madurai – 625002, TamilNadu, India*
[8] *Department of Botany, Government Arts College, Melur – 625106, Madurai, TamilNadu, India*

Article Info:

Article History:

Received 22 March 2022
Reviewed 01 April 2022
Accepted 06 April 2022
Published 15 April 2022

Cite this article as:

Ramya S, Loganathan T, Chandran M, Priyanka R, Kavipriya K, Grace Lydial Pushpalatha G, Aruna D, Abraham GC, Jayakumararaj R, ADME-Tox profile of Cuminaldehyde (4-Isopropylbenzaldehyde) from *Cuminum cyminum* seeds for potential biomedical applications, Journal of Drug Delivery and Therapeutics. 2022; 12(2-s):127-141

DOI: http://dx.doi.org/10.22270/jddt.v12i2-s.5286

*Address for Correspondence:

R. Jayakumararaj, Department of Botany, Government Arts College, Melur – 625106, Madurai, TamilNadu, India

Abstract

Cuminum cyminum L (Family: Apiaceae) is a small multipurpose herb. Seeds of cumin are widely used as a spice for its distinctive aroma, and more commonly in various indigenous traditional systems of medicine. Access through web literature provides ample evidence for biomedical activities of *Cuminum cyminum* seeds (CCS). CCS has been used in traditional medicine to treat variety of diseases, including hypolipidemia, cancer, and diabetes. Biomedical properties of CCS is attributed to its phytochemical class of compounds viz., terpenes, phenols and flavonoids. Health effects of CCS have been experimentally validated through phytochemical screening deciphering the fact that it contains a large number of bioactive secondary metabolites (BASMs) viz., alkaloid, coumarin, anthraquinones, flavonoid, glycoside, protein, resin, saponin, tannin and steroid. Furthermore, pharmacological studies indicate that BASMs in CCS exert antimicrobial, insecticidal, anti-inflammatory, analgesic, antioxidant, anticancer, antidiabetic, anti-platelet-aggregation, hypotensive, bronchodilatory, immunological, contraceptive, anti-amyloidogenic, anti-osteoporotic, aldose reductase, α-glucosidase and tyrosinase inhibitory effects. Cuminaldehyde is one of the major bioactive compounds in CCS that holds significant pharmacological prominence. However, in-depth studies are lacking henceforth warranted to elucidate and fill the gaps, particularly on phytocompound isolation, pre-clinical, clinical characterization, and evaluation of structure–activity relationship. The present study prospects ADMETox perspectives of cuminaldehyde (4-Isopropylbenzaldehyde).

Keywords: Cuminaldehyde; Isopropylbenzaldehyde; *Cuminum cyminum;* ADMETox; Natural Product (NP)

INTRODUCTION

Drug development is a lengthy, complex, and costly process, entrenched with a high degree of uncertainty that a drug will actually succeed to reach the market or not. Drug development process can be divided into several stages, including disease-related genomics, target identification/ validation, lead discovery/ optimization, preclinical/ clinical trials[1]. During early stages of drug discovery and development, activities and specificities of candidate drug lead molecule is assessed at an early stage pharmacokinetics and late stage toxicity[2]. Practically, most of the time, withdrawal of a proven candidate drug lead in the final stage is ascribed to some undesirable efficacy/ safety in absorption, distribution, metabolism, excretion and toxicity (ADMET)[3-6].

Cook et al.[7] comprehensively reviewed the results of AstraZeneca's small-molecule drug projects from 2005 to 2010 based on a longitudinal study and pointed out that unacceptable safety and toxicity were the most important reasons for the failure of more than half of all projects undertaken. Potential compounds, for example, can be generated through binding/ functional, biochemical, and cellular or cytotoxicity assays. High-throughput screening through a large compound library can identify multiple compounds. Progressing to a lead compound(s) can involve complex cellular assays, toxicological surrogate assays, bio-pharmacological surrogates, and surrogates for absorption, distribution, metabolism, and excretion (ADME)[3,5,6]. As with the development of drug discovery, it was realized that it is important to filter and optimize the properties for drugs at an early stage, which has been accepted and widely used to reduce the attrition rate in drug research and development. A Fail-Early-Fail-Cheap strategy is employed by many of the pharmaceutical companies[8]. Pharmacokinetics and toxicity assessments of preclinical drugs are of significant value in reducing the failure rate of new chemical entities in clinical trials.[6,9,10]

In recent years, *in vitro* and *in vivo* ADMET prediction methods have been widely used[5,6,11-17], but it is almost impractical to perform complex/ expensive experiments on a large number of compounds[5,18]. Thus, *in silico* ADMET predict has turn out to be an attractive Cost-Saving High-Throughput alternative to conventional methods.[14,16,18]

Natural products (NPs) from medicinal plants and their structural analogues have made significant contribution to pharmacotherapy, especially for the treatment of cancer and infectious diseases.[19-24] Nevertheless, NPs present challenges for drug discovery, such as technical barriers to screening, isolation, characterization and optimization, with a decline in their pursuit by pharma-industries since 1990s.[22]

Cuminum cyminum a small herbaceous medicinal plant, it has tropical distribution, however, more common to Egypt, the Mediterranean, and SEA countries with culinary and traditional pharmacological uses.[25] In traditional medicine, cumin seeds were used to treat hoarseness, jaundice, dyspepsia and diarrhoea. Traditionally the seeds were used for stomachic, diuretic, carminative, stimulant, astringent and abortifacient properties.[25] In Unani system of medicine, fruits of *C. cyminum* are used as an astringent, carminative, emmenagogue, for the treatment of corneal opacities, ulcers, boils, relieve cough and metabolic inflammation.[26] Furthermore, cumin oil is used in perfumery and as a seasoning agent in food preparations.[25,26] Bioactive natural products in the CCS extracts exhibit a wide range of pharmacological activities.[25,27]

Phytochemical analysis of *C. cyminum* revealed that it contains alkaloid, coumarin, anthraquinone, flavonoid, glycoside, protein, resin, saponin, tannin and steroid[28]. Pharmacological studies have proven that CCS exerts antimicrobial, insecticidal, anti-inflammatory, analgesic, antioxidant, anticancer, antidiabetic, antiplatelet aggregation, hypotensive, bronchodilatory, immunological, contraceptive, anti-amyloidogenic, anti-osteoporotic, aldose reductase , α-glucosidase and tyrosinase inhibitory effects. GCMS analysis revealed the presence of several bioactive compounds, of which cuminaldehyde was identified as the principle compound. Cuminaldehyde (CA) (Fig. 1) is an aromatic monoterpenoid volatile compound, a natural p-isopropyl-benzaldehyde, activate compound of essential oil from eucalyptus[29], myrrh[29], caraway[30], Chinese cinnamon[30]. Structurally, CA is a benzaldehyde substituted at the 4th position with an isopropyl group. Commercially CA is used in perfumes and cosmetics due to its pleasant aroma. CA has antidiabetic[31], antitumor[32], anti-inflammatory[33], antimicrobial[34], and antifungal[35] effects. Studies depict that CA exerts protective effect against neuro-degenerative diseases (Parkinson's disease).[36] Recently, it has been demonstrated that dietary administration of cumin-derived-CA induce neuroprotective, learning and memory enhancement effects in the experimental model.[37]

MATERIALS AND METHODS

vNN method rests on the concept that compounds with similar structures have similar activities. It is therefore reasonable to weight the contributions of neighbours so that closer neighbours contribute more to the predicted value. The vNN method calculates the similarity distance between molecules in terms of their structure, and uses a distance threshold to define a domain of applicability (i.e., all nearest neighbors that meet a minimum similarity threshold constraint). This applicability domain ensures that the predictions generated are reliable. vNN models can be built within minutes and require no re-training when new assay information becomes available—an important feature when keeping quantitative structure–activity relationship (QSAR) models up-to-date to maintain their performance levels. The performance characteristics of vNN-based models are comparable, and often superior to, those of other more elaborate model constructs. One of the most widely used measures of the similarity distance between two small molecules is the Tanimoto distance, d, which is defined as:

$$d = 1 - \frac{n(P \cap Q)}{n(P) + n(Q) - n(P \cap Q)},$$

where η(P∩Q) is the number of features common to molecules p and q, and η(P) and η(Q) are the total numbers of features for molecules p and q, respectively. The predicted biological activity y is then given by a weighted average across structurally similar neighbours:

$$y = \frac{\sum_{i=1}^{v} y_i e^{-\left(\frac{d_i}{h}\right)^2}}{\sum_{i=1}^{v} e^{-\left(\frac{d_i}{h}\right)^2}}, \quad d_i \le d_0,$$

where d_i denotes the Tanimoto distance between a query molecule for which a prediction is made and a molecule i of the training set; d_0 is a Tanimoto-distance threshold, beyond which two molecules are no longer considered to be sufficiently similar to be included in the average; y_i is the experimentally measured activity of molecule i; v denotes the total number of molecules in the training set that satisfies the condition $d_i \le d_0$; and h is a smoothing factor, which dampens the distance penalty. The values of h and d_0 are determined from cross-validation studies. To identify structurally similar compounds, were used Accelrys extended-connectivity fingerprints with a diameter of four chemical bonds (ECFP4), which have previously been reported to show good overall performance.

Model Validation

A 10-fold cross-validation (CV) procedure was used to validate new models and to determine the values of the smoothing factor h and Tanimoto distance d_0. In this procedure, the data was randomly divided into 10 sets, and used 9 to develop the model and the 10th to validate it. This process was repeated 10 times, leaving each set of molecules out once. When building new models, averages of the 10-fold CV was reported as the performance measures.

Performance Measures

Metrics to assess model performance were (1) sensitivity measures a model's ability to correctly detect true positives, (2) specificity measures a model's ability to detect true negatives, (3) accuracy measures a model's ability to make correct predictions , and (4) kappa compares the probability of correct predictions to the probability of correct predictions by chance (its value ranges from +1 (perfect agreement between model prediction and experiment) to −1 (complete disagreement), with 0 indicating no agreement beyond that expected by chance).

$$\text{sensitivity} = \frac{TP}{TP + FN}$$

$$\text{specificity} = \frac{TN}{FP + TN}$$

$$\text{accuracy} = \frac{TP + TN}{TP + TN + FP + FN}$$

$$\text{kappa} = \frac{\text{accuracy} - Pr(e)}{1 - Pr(e)}$$

where TP, TN, FP, and FN denote the numbers of true positives, true negatives, false positives, and false negatives, respectively. Kappa is a metric for assessing the quality of binary classifiers. Pr(e) is an estimate of the probability of a correct prediction by chance. It is calculated as:

$$Pr(e) = \frac{(TP + FN)(TP + FP) + (FP + TN)(TN + FN)}{(TP + FN + FP + TN)^2}$$

The calculated coverage is the proportion of test molecules with at least one nearest neighbour that meets the similarity criterion. The coverage is a measure of how many test compounds are within the applicability domain of a prediction model.

RESULTS AND DISCUSSION

Studies indicate that hunt, identification and biomolecular characterisation of the plant derived natural products remains the mainstay prerequisite for use of NPs in the pharma-industries.[39-49]

Chemical kingdom	:	Organic compounds
Super class	:	Lipids and lipid-like molecules
Class	:	Prenol lipids
Subclass	:	Monoterpenoids
PubChem Identifier	:	326
ChEBI Identifier	:	28671
CAS Identifier	:	122-03-2
Synonyms	:	LEUCOPELARGONIDIN
Canonical SMILES	:	O=CC1CCC(CC1)C(C)C
InChI Key	:	WTWBUQJHJGUZCY-UHFFFAOYSA-N

Liver Toxicity DILI

Drug-induced liver injury (DILI) is considered as one of the most commonly cited reasons for drug withdrawals from the market[50]. A vNN-based LT-DILI prediction model indicates whether a compound could cause DILI. The dataset of 1,431 compounds was obtained from online sources containing dataset both pharmaceuticals and non-pharmaceuticals and classified a compound as causing DILI if it was associated with a high risk of DILI and not if there was no such risk. Prediction report obtained for the LT-DILI prediction model has been provided (Fig.3a; Table 2b).

Cytotoxicity (HepG2)

Cytotoxicity is the degree to which a chemical causes damage to cells.[51] A cytotoxicity prediction model was developed, using in vitro data on toxicity against HepG2 cells for 6,000 structurally diverse compounds, which were collected from ChEMBL. In developing our model, compounds with an IC50 ≤ 10 µM in the in vitro assay were considered as cytotoxic (Fig.3b; Table 2b).

Metabolism HLM

Human liver microsomal (HLM) stability assay is commonly used to identify and exclude compounds that are too rapidly metabolized. For a drug to achieve effective therapeutic concentrations in the body, it cannot be metabolized too rapidly by the liver.[52] Compounds with a half-life of 30 minutes or longer in an HLM assay are considered as stable; otherwise they are considered unstable. HLM data was retrieved from the ChEMBL database, manually curated the data, and classified compounds as stable or unstable based on the reported half-life ($T_{1/2}$ > 30 min was considered stable, and $T_{1/2}$ < 30 min unstable.[53] The final dataset contained 3,654 compounds. Of these, 2,313 compounds were classified as stable and 1,341 as unstable (Fig.3c; Table 2b).

Cytochrome P450 enzyme (CYP) inhibition

CYPs constitute a superfamily of proteins that play an important role in the metabolism and detoxification of xenobiotics. In vitro data derived from five main drug-metabolizing CYPs—1A2, 3A4, 2D6, 2C9, and 2C19 were used to develop CYP inhibition models. We retrieved CYP inhibitors from PubChem and classified a compound with an IC50 ≤ 10 µM for an enzyme as an inhibitor of the enzyme. Data provides predictions for the following enzymes: CYP1A2, CYP3A4, CYP2D6, CYP2C9, and CYP2C19 (Fig.3d; Table 2b).

Membrane Transporters BBB

Blood-brain barrier (BBB) is a highly selective barrier that separates the circulating blood from the central nervous system.[54,55] A vNN-based BBB model was developed, using 352 compounds whose BBB permeability values (log BB) were obtained from the literature respectively. Compounds with log BB values of less than −0.3 and greater than +0.3 were classified as BBB non-permeable and permeable (Fig.3e; Table 2b).

Pgp Substrates and Inhibitors

P-glycoprotein (Pgp) is an essential cell membrane protein that extracts many foreign substances from the cell.[56] Cancer cells often overexpress Pgp, which increases the efflux of chemotherapeutic agents from the cell and prevents treatment by reducing the effective intracellular concentrations of such agents - a phenomenon known as multidrug resistance. For this reason, identifying compounds that can either be transported out of the cell by Pgp (substrates) or impair Pgp function (inhibitors) is of great interest. In the present study models were developed to predict both Pgp substrates and Pgp inhibitors. This dataset consists of measurements of 422 substrates and 400 non-substrates. To generate a large Pgp inhibitor dataset, two datasets were combined and duplicates were removed to form a combined dataset consisting of a training set of 1,319 inhibitors and 937 non-inhibitors (Fig.3f; Table 2b).

hERG (Cardiotoxicity)

Human ether-à-go-go-related gene (hERG) codes for a potassium ion channel involved in the normal cardiac repolarization activity of the heart.[57] Drug-induced blockade of hERG function can cause long QT syndrome that may result in arrhythmia and death. As much as 282 known hERG blockers retrieved from the literature and classified compounds with an IC_{50} cut-off value of 10 µM or less as blockers. This study used a set of 404 compounds with IC_{50} values greater than 10 µM from ChEMBL and classified them as non-blockers (Fig.3g; Table 2b).

MMP (Mitochondrial Toxicity)

Fundamental role of mitochondria in cellular energetics and oxidative stress, mitochondrial dysfunction has been implicated in cancer, diabetes, neurodegenerative disorders, and cardiovascular diseases. Largest dataset of chemical-induced changes has been used to understand the mitochondrial membrane potential (MMP), based on the assumption that a compound that causes mitochondrial dysfunction is also likely to reduce the MMP. vNN-based MMP prediction model was developed using 6,261 compounds collected from a previous study that screened a library of

10,000 compounds (~8,300 unique chemicals) at 15 concentrations, each in triplicate, to measure changes in the MMP in HepG2 cells. Prediction analysis data obtained indicate that 913 compounds decreased the MMP, whereas 5,395 compounds had no effect (Fig.3h; Table 2b).

Mutagenicity (Ames test)

It has been well established that mutagens cause abnormal genetic mutations leading to cancer. A common way to assess a chemical's mutagenicity is the Ames test. Prediction model has been developed, using a literature dataset of 6,512 compounds, of which 3,503 were Ames-positive (Fig.3i; Table 2b).

Maximum Recommended Therapeutic Dose (MRTD)

MRTD is an estimated upper daily dose that is safe. The model built as a prediction model based on a dataset of MRTD values [58]publically disclosed by the FDA, mostly of single-day oral doses for an average adult with a body weight of 60 kg, for 1,220 compounds (most of which are small organic drugs). In theis model organometallics were excluded, high-molecular weight polymers (>5,000 Da), nonorganic chemicals, mixtures of chemicals, and very small molecules (<100 Da). An external test set of 160 compounds that were used were collected by the FDA for validation. The total dataset for our model contained 1,185 compounds. Predicted MRTD value is reported in mg/day unit based upon an average adult weighing 60 kg (Fig.3j; Table 2b). The summary of physiochemical and biomolecular properties of CA is given in table 3.

CONCLUSION

In-silico data supports the traditional claims towards CCS - cuminaldehyde at the same time warrants experimental proof to enhance the untapped market potential of this NP.

REFERENCES

1. Attene-Ramos, M., R. Huang, S. Michael, K. Witt, A. Richard, R. Tice, A. Simeonov, C. Austin, M. Xia. Profiling of the Tox21 chemical collection for mitochondrial function to identify compounds that acutely decrease mitochondrial membrane potential. 2015; 123(1):49. https://doi.org/10.1289/ehp.1408642

2. Broccatelli, F., E. Carosati, A. Neri, M. Frosini, L. Goracci, T. Oprea, and G. Cruciani. A novel approach for predicting P-Glycoprotein (ABCB1) inhibition using molecular interaction fields. 2011; 54(6):1740-1751. https://doi.org/10.1021/jm101421d

3. Caldwell GW, Yan Z, Tang W, Dasgupta M, Hasting B. ADME optimization and toxicity assessment in early-and late-phase drug discovery. Current topics in medicinal chemistry. 2009; 9(11):965-80. https://doi.org/10.2174/156802609789630929

4. Chen, L., Y. Li, Q. Zhao, H. Peng, and T. Hou. ADME evaluation in drug discovery. 10. Predictions of P-Glycoprotein inhibitors using recursive partitioning and naive bayesian classification techniques. 2011; 8(3):889-900. https://doi.org/10.1021/mp100465q

5. Cheng F, Li W, Liu G, Tang Y. In silico ADMET prediction: recent advances, current challenges and future trends. Current topics in medicinal chemistry. 2013; 13(11):1273-89. https://doi.org/10.2174/15680266113139990033

6. Ferreira LL, Andricopulo AD. ADMET modelling approaches in drug discovery. Drug discovery today. 2019; 24(5):1157-1165. https://doi.org/10.1016/j.drudis.2019.03.015

7. Cook D, Brown D, Alexander R, March R, Morgan P, Satterthwaite G, Pangalos MN. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. Nature reviews Drug discovery. 2014; 13(6):419-431. https://doi.org/10.1038/nrd4309

8. Yu H, Adedoyin A. ADME-Tox in drug discovery: integration of experimental and computational technologies. Drug discovery today. 2003; 8(18):852-61. https://doi.org/10.1016/S1359-6446(03)02828-9

9. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates?. Nature reviews Drug discovery. 2004; 3(8):711-6. https://doi.org/10.1038/nrd1470

10. Yang H, Sun L, Li W, Liu G, Tang Y. In silico prediction of chemical toxicity for drug design using machine learning methods and structural alerts. Frontiers in chemistry. 2018; 6:30. https://doi.org/10.3389/fchem.2018.00030

11. Kandeepan C, Kalaimathi RV, Jeevalatha A, Basha AN, Ramya S, Jayakumararaj R. In-silico ADMET Pharmacoinformatics of Geraniol (3,7-dimethylocta-trans-2,6-dien-1-ol)-acyclic monoterpene alcohol drug from Leaf Essential Oil of Cymbopogon martinii from Sirumalai Hills (Eastern Ghats), INDIA. Journal of Drug Delivery and Therapeutics. 2021; 11(4-S):109-18. https://doi.org/10.22270/jddt.v11i4-S.4965

12. Li, D., L. Chen, Y. Li, S. Tian, H. Sun, and T. Hou. ADMET evaluation in drug discovery. Development of in Silico prediction models for P-Glycoprotein substrates. 2014; 11(3):716-726. https://doi.org/10.1021/mp400450m

13. Loganathan T, Barathinivas A, Soorya C, Balamurugan S, Nagajothi TG, Ramya S, Jayakumararaj R. Physicochemical, Druggable, ADMET Pharmacoinformatics and Therapeutic Potentials of Azadirachtin-a Prenol Lipid (Triterpenoid) from Seed Oil Extracts of Azadirachta indica A. Juss. Journal of Drug Delivery and Therapeutics. 2021; 11(5):33-46. https://doi.org/10.22270/jddt.v11i5.4981

14. Schyman, P., R. Liu, V. Desai, and A. Wallqvist. vNN web server for ADMET predictions. Frontiers in Pharmacology. 2017; 8:889. https://doi.org/10.3389/fphar.2017.00889

15. Selick HE, Beresford AP, Tarbit MH. The emerging importance of predictive ADME simulation in drug discovery. Drug Discovery Today. 2002; 7(2):109-16. https://doi.org/10.1016/S1359-6446(01)02100-6

16. Sabitha M, Krishnaveni K, Murugan M, Basha AN, Pallan GA, Kandeepan C, Ramya S, Jayakumararaj R. In-silico ADMET predicated Pharmacoinformatics of Quercetin-3-Galactoside, polyphenolic compound from Azadirachta indica, a sacred tree from Hill Temple in Alagarkovil Reserve Forest, Eastern Ghats, INDIA. Journal of Drug Delivery and Therapeutics. 2021; 11(5-S):77-84. https://doi.org/10.22270/jddt.v11i5-S.5026

17. Soorya C, Balamurugan S, Ramya S, Neethirajan K, Kandeepan C, Jayakumararaj R. Physicochemical, ADMET and Druggable properties of Myricetin: A Key Flavonoid in Syzygium cumini that regulates metabolic inflammations. Journal of Drug Delivery and Therapeutics. 2021; 11(4):66-73. https://doi.org/10.22270/jddt.v11i4.4890

18. Ramya S, Soorya C, Sundari A, Grace Lydial Pushpalatha G, Aruna D, Loganathan T, Balamurugan S, Abraham GC, Ponrathy T, Kandeepan C, Jayakumararaj R, Artificial Intelligence and Machine Learning approach based in-silico ADME-Tox and Pharmacokinetic Profile of α-Linolenic acid from Catharanthus roseus (L.) G. Don., Journal of Drug Delivery and Therapeutics. 2022; 12(2-s):96-109. https://doi.org/10.22270/jddt.v12i2-S.5274

19. Cragg GM, Newman DJ. Natural products: a continuing source of novel drug leads. Biochimica et Biophysica Acta (BBA)-General Subjects. 2013 Jun 1; 1830(6):3670-95. https://doi.org/10.1016/j.bbagen.2013.02.008

20. Thomford NE, Senthebane DA, Rowe A, Munro D, Seele P, Maroyi A, Dzobo K. Natural products for drug discovery in the 21st century: innovations for novel drug discovery. International journal of molecular sciences 2018; 19(6):1578. https://doi.org/10.3390/ijms19061578

21. Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. Journal of

Natural Products. 2020; 83(3):770-803. https://doi.org/10.1021/acs.jnatprod.9b01285

22. Atanasov AG, Zotchev SB, Dirsch VM, Supuran CT. Natural products in drug discovery: advances and opportunities. Nature Reviews Drug Discovery 2021; 20(3):200-16. https://doi.org/10.1038/s41573-020-00114-z

23. Shanmugam S, Sundari A, Muneeswaran S, Vasanth C, Jayakumararaj R, Rajendran K. Ethnobotanical indices on medicinal plants used to treat poisonous bites in Thiruppuvanam region of Sivagangai district in Tamil Nadu, India. Journal of Drug Delivery and Therapeutics. 2020; 10(6-s):31-36. https://doi.org/10.22270/jddt.v10i6-s.4432

24. Kadhirvel K, Ramya S, Sudha TS, Ravi AV, Rajasekaran C, Selvi RV, Jayakumararaj R. Ethnomedicinal survey on plants used by tribals in Chitteri Hills. Environ We Int J Sci Tech. 2010; 5:35-46.

25. Kalaivani T, Premkumar N, Ramya S, Siva R, Vijayakumar V, Meignanam E, Rajasekaran C, Jayakumararaj R. Investigations on hepatoprotective activity of leaf extracts of Aegle marmelos (L.) Corr. (Rutaceae). Ethnobotanical leaflets. 2009; 2009(1):4.

26. Ramya S, Alaguchamy N, Maruthappan VM, Sivaperumal R, Sivalingam M, Krishnan A, Govindaraji V, Kannan K, Jayakumararaj R. Wound healing ethnomedicinal plants popular among the Malayali tribes in Vattal Hills, Dharmapuri, TN, India. Ethnobotanical Leaflets. 2009; 2009(10):6.

27. Ramya S, Jayakumararaj R. Antifeedant activity of selected ethno-botanicals used by tribals of Vattal Hills on Helicoverpa armigera (Hübner). Journal of Pharmacy Research. 2009; 2(8):1414-8.

28. Ramya S, Jepachanderamohan PJ, Kalayanasundaram M, Jayakumararaj R. In vitro antibacterial prospective of crude leaf extracts of Melia azedarach Linn. against selected bacterial strains. Ethnobotanical Leaflets. 2009; 2009(1):32.

29. Ramya S, Krishnasamy G, Jayakumararaj R, Periathambi N, Devaraj A. Bioprospecting Solanum nigrum Linn.(Solanaceae) as a potential source of Anti-Microbial agents against selected Bacterial strains. Asian Journal of Biomedical and Pharmaceutical Sciences. 2012; 2(12):65.

30. Ramya S, Neethirajan K, Jayakumararaj R. Profile of bioactive compounds in Syzygium cumini-a review. Journal of Pharmacy research. 2012; 5(8):4548-53.

31. Sivaperumal R, Ramya S, Ravi AV, Rajasekaran C, Jayakumararaj R. Herbal remedies practiced by Malayali's to treat skin diseases. Environ We Int J Sci Tech. 2009; 4(1):35-44.

32. Sivaperumal R, Ramya S, Ravi AV, Rajasekaran C, Jayakumararaj R. Ethnopharmacological studies on the medicinal plants used by tribal inhabitants of Kottur Hills, Dharmapuri, Tamilnadu, India. Environ We Int J Sci Technol. 2010; 5:57-64.

33. Soorya C, Balamurugan S, Basha AN, Kandeepan C, Ramya S, Jayakumararaj R. Profile of Bioactive Phyto-compounds in Essential Oil of Cymbopogon martinii from Palani Hills, Western Ghats, INDIA. Journal of Drug Delivery and Therapeutics. 2021; 11(4):60-5. https://doi.org/10.22270/jddt.v11i4.4887

34. Sundari A, Jayakumararaj R. Herbal remedies used to treat skin disorders in Arasankulam region of Thoothukudi District in Tamil Nadu, India. Journal of Drug Delivery and Therapeutics. 2020; 10(5):33-38. https://doi.org/10.22270/jddt.v10i5.4277

35. Sundari A, Jayakumarbaraj R. Medicinal plants used to cure cuts and wounds in Athur region of Thoothukudi district in Tamil Nadu, India. Journal of Drug Delivery and Therapeutics. 2020; 10(6-s):26-30. https://doi.org/10.22270/jddt.v10i6-s.4429

36. Yuan H, Ma Q, Ye L, Piao G. The traditional medicine and modern medicine from natural products. Molecules. 2016; 21(5):559. https://doi.org/10.3390/molecules21050559

37. Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P, Temml V, Wang L, Schwaiger S, Heiss EH, Rollinger JM. Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnology advances 2015; 33(8):1582-614. https://doi.org/10.1016/j.biotechadv.2015.08.001

38. Omari Z, Kazunori S, Sabti M, Bejaoui M, Hafidi A, Gadhi C, Isoda H. Dietary administration of cumin-derived cuminaldehyde induce neuroprotective and learning and memory enhancement effects to aging mice. Aging (Albany NY). 2021; 13(2):1671. https://doi.org/10.18632/aging.202516

39. Al-Snafi AE. The pharmacological activities of Cuminum cyminum A review. IOSR Journal of Pharmacy. 2016; 6(6):46-65.

40. Mnif S, Aifa S. Cumin (Cuminum cyminum L.) from traditional uses to potential biomedical applications. Chemistry & biodiversity. 2015 May; 12(5):733-42. https://doi.org/10.1002/cbdv.201400305

41. Patel CN, Kumar SP, Rawal RM, Patel DP, Gonzalez FJ, Pandya HA. A multi-parametric organ toxicity predictor for drug discovery. Toxicology mechanisms and methods. 2020; 30(3):159-66. https://doi.org/10.1080/15376516.2019.1681044

42. Ramya S, Loganathan T, Chandran M, Priyanka R, Kavipriya D, Grace Lydial Pushpalatha G, Aruna D, Ramanathan L, Jayakumararaj R, Phytochemical Screening, GCMS, FTIR profile of Bioactive Natural Products in the methanolic extracts of Cuminum cyminum seeds and oil, Journal of Drug Delivery and Therapeutics. 2022; 12(2-s):110-118. https://doi.org/10.22270/jddt.v12i2-S.5280

43. Nyberg L, Backman L. Cognitive ageing: a view from brain imaging. In: Dixon R, Backman L, Nilsson L, Eds. New frontiers in cognitive ageing. Oxford University Press, 2004; 135-60. https://doi.org/10.1093/acprof:oso/9780198525691.003.0007

44. Ebada ME. Cuminaldehyde: A potential drug candidate. J Pharmacol Clin Res. 2017; 2(2):1-4. https://doi.org/10.19080/JPCR.2017.02.555585

45. Jabeen NS, Jagapriya L, Senthilkumar B, Devi K. Challenging Compounds of Some Medicinal Plants against Cancer. Drug Development for Cancer and Diabetes: A Path to 2030. 2020 Aug 30:95. https://doi.org/10.1201/9780429330490-8

46. Tomy MJ, Dileep KV, Prasanth S, Preethidan DS, Sabu A, Sadasivan C, Haridas M. Cuminaldehyde as a lipoxygenase inhibitor: in vitro and in silico validation. Applied biochemistry and biotechnology. 2014 Sep; 174(1):388-97. https://doi.org/10.1007/s12010-014-1066-0

47. Monteiro-Neto V, de Souza CD, Gonzaga LF, da Silveira BC, Sousa NC, Pontes JP, Santos DM, Martins WC, Pessoa JF, Carvalho Junior AR, Almeida VS. Cuminaldehyde potentiates the antimicrobial actions of ciprofloxacin against Staphylococcus aureus and Escherichia coli. PLoS One. 2020 May 14; 15(5):e0232987. https://doi.org/10.1371/journal.pone.0232987

48. Hassan HA, Genaidy MM, Kamel MS, Abdelwahab SF. Synergistic antifungal activity of mixtures of clove, cumin and caraway essential oils and their major active components. Journal of Herbal Medicine. 2020 Dec 1; 24:100399. https://doi.org/10.1016/j.hermed.2020.100399

49. Morshedi D, Aliakbari F, Tayaranian-Marvian A, Fassihi A, Pan-Montojo F, Pérez-Sánchez H. Cuminaldehyde as the major component of Cuminum cyminum, a natural aldehyde with inhibitory effect on alpha-synuclein fibrillation and cytotoxicity. Journal of food science. 2015; 80(10):H2336-45. https://doi.org/10.1111/1750-3841.13016

50. Xu, Y., Z. Dai, F. Chen, S. Gao, J. Pei, and L. Lai. Deep learning for drug-induced liver injury. 2015; 55 (10):2085-2093 https://doi.org/10.1021/acs.jcim.5b00238

51. Liu, R., and A. Wallqvist. Merging applicability domains for in silico assessment of chemical mutagenicity. Journal of Chemical Information and Modelling. 2014; 54(3):793-800. https://doi.org/10.1021/ci500016v

52. Liu, R., P. Schyman, and A. Wallqvist. Critically assessing the predictive power of QSAR models for human liver microsomal stability. Journal of Chemical Information and Modelling. 2015; 55(8):1566-1575. https://doi.org/10.1021/acs.jcim.5b00255

53. Loganathan T, Barathinivas A, Soorya C, Balamurugan S, Nagajothi TG, Jayakumararaj R. GCMS Profile of Bioactive Secondary Metabolites with Therapeutic Potential in the Ethanolic Leaf Extracts of Azadirachta indica: A Sacred Traditional Medicinal Plant of INDIA. Journal of Drug Delivery and Therapeutics. 2021; 11(4-S):119-26. https://doi.org/10.22270/jddt.v11i4-S.4967

54. Muehlbacher, M., G. Spitzer, K. Liedl, J. Kornhuber. Qualitative prediction of blood-brain barrier permeability on a large and refined dataset. Journal of Computer-Aided Molecular Design. 2011; 25:1095. https://doi.org/10.1007/s10822-011-9478-1

55. Naef R. A generally applicable computer algorithm based on the group additively method for the calculation of seven molecular descriptors: Heat of combustion, LogPO/W, LogS, refractivity, polarizability, toxicity and LogBB of organic compounds; scope and limits of applicability. Molecules. 2015; 20(10):18279-351. https://doi.org/10.3390/molecules201018279

56. Schyman, P., R. Liu, and A. Wallqvist. Using the variable-nearest neighbour method to identify P-glycoprotein substrates and inhibitors. ACS Omega. 2016; 1(5):923-929. https://doi.org/10.1021/acsomega.6b00247

57. Schyman, P., R. Liu, and A. Wallqvist. General purpose 2D and 3D similarity approach to identify hERG blockers. Journal of Chemical Information and Modelling. 2016; 56(1):213-222. https://doi.org/10.1021/acs.jcim.5b00616

58. Liu, R., G. Tawa, and A. Wallqvist. Locally weighted learning methods for predicting dose-dependent toxicity with application to the human maximum recommended daily dose. Chemical Research in Toxicology. 2012; 25(10):2216-2226.

Table 1: Physicochemical, druggability, ADMET properties of Cuminaldehyde

PHYSICOCHEMICAL PROPERTIES		VALUE
Molecular weight		148.21 g/mol
LogP		2.62
LogD		2.93
LogSw		-2.48
Number of stereocenters		0
Stereochemical complexity		0.000
Fsp3		0.300
Topological polar surface area		17.07 Å^2
Number of hydrogen bond donors		0
Number of hydrogen bond acceptors		1
Number of smallest set of smallest rings (SSSR)		1
Size of the biggest system ring		6
Number of rotatable bonds		2
Number of rigid bonds		7
Number of charged groups		0
Total charge of the compound		0
Number of carbon atoms		10
Number of heteroatoms		1
Number of heavy atoms		11
Ratio between the number of non-carbon atoms and carbon atoms		0.1
DRUGGABILITY PROPERTIES		**VALUE**
Lipinski's rule of 5 violations		0
Veber rule		Good
Egan rule		Good
Oral PhysChem score (Traffic Lights)		0
GSK's 4/400 score		Good
Pfizer's 3/75 score		Warning
Weighted quantitative estimate of drug-likeness (QEDw) score		0.589
Solubility		12450.74
Solubility Forecast Index		Good
ADMET PROPERTIES	**DESCRIPTION**	**PROBABILITY**
Human Intestinal Absorption	HIA+	1.000
Blood Brain Barrier	BBB+	0.976
Caco-2 permeable	Caco2+	0.916
P-glycoprotein substrate	Non-substrate	0.736
P-glycoprotein inhibitor I	Non-inhibitor	0.963
P-glycoprotein inhibitor II	Non-inhibitor	0.989
CYP450 2C9 substrate	Non-substrate	0.798
CYP450 2D6 substrate	Non-substrate	0.930
CYP450 3A4 substrate	Non-substrate	0.721
CYP450 1A2 inhibitor	Non-inhibitor	0.679
CYP450 2C9 inhibitor	Non-inhibitor	0.946
CYP450 2D6 inhibitor	Non-inhibitor	0.952
CYP450 2C19 inhibitor	Non-inhibitor	0.965
CYP450 3A4 inhibitor	Non-inhibitor	0.975
CYP450 inhibitory promiscuity	Low CYP Inhibitory Promiscuity	0.892
Ames test	Non AMES toxic	0.981
Carcinogenicity	Non-carcinogens	0.510
Biodegradation	Ready biodegradable	0.587
Rat acute toxicity	1.901 LD50, mol/kg	NA
hERG inhibition (predictor I)	Weak inhibitor	0.963
hERG inhibition (predictor II)	Non-inhibitor	0.965

Table 2a: Color coded matrix of vNN models in 10-fold cross validation using a restricted/ unrestricted applicability domain

Note: Prediction was conducted in conjunction with the Telemedicine and Advanced Technology Research Center (TATRC) and US Army Medical Research and Development Command (USAMRDC).

Table 2b: Summary of performance analysis of vNN models in 10-fold cross validation using a restricted/ unrestricted applicability domain

MODEL	Data[a]	d_0[b]	h[c]	Accuracy	Sensitivity	Specificity	kappa	R[d]	Coverage
DILI	1427	0.6	0.5	0.71	0.7	0.73	0.42	0.00	0.66
		1.0	0.2	0.67	0.62	0.72	0.34	0.00	1.00
Cytotox (hep2g)	6097	0.4	0.2	0.84	0.88	0.76	0.64	0.00	0.89
		1.0	0.2	0.84	0.73	0.89	0.62	0.00	1.00
HLM	3219	0.4	0.2	0.81	0.72	0.87	0.59	0.00	0.91
		1.0	0.2	0.81	0.7	0.87	0.57	0.00	1.00
CYP1A2	7558	0.5	0.2	0.9	0.7	0.95	0.66	0.00	0.75
		1.0	0.2	0.89	0.61	0.95	0.6	0.00	1.00
CYP2C9	8072	0.5	0.2	0.91	0.55	0.96	0.54	0.00	0.76
		1.0	0.2	0.9	0.44	0.96	0.46	0.00	1.00
CYP2C19	8155	0.55	0.2	0.87	0.64	0.93	0.58	0.00	0.76
		1.0	0.2	0.86	0.52	0.94	0.5	0.00	1.00
CYP2D6	7805	0.5	0.2	0.89	0.61	0.94	0.57	0.00	0.75
		1.0	0.2	0.88	0.52	0.95	0.51	0.00	1.00
CYP3A4	10373	0.5	0.2	0.88	0.76	0.92	0.68	0.00	0.78
		1.0	0.2	0.88	0.69	0.93	0.64	0.00	1.00
BBB	353	0.6	0.2	0.9	0.94	0.86	0.8	0.00	0.61
		1.0	0.1	0.82	0.88	0.75	0.64	0.00	1.00
Pgp Substrate	822	0.6	0.2	0.79	0.8	0.79	0.58	0.00	0.66
		1.0	0.2	0.73	0.73	0.74	0.47	0.00	1.00
Pgp Inhibitor	2304	0.5	0.2	0.85	0.91	0.73	0.66	0.00	0.76
		1.0	0.1	0.81	0.86	0.74	0.61	0.00	1.00
hERG	685	0.7	0.7	0.84	0.84	0.83	0.68	0.00	0.8
		1.0	0.2	0.82	0.82	0.83	0.64	0.00	1.00
MMP	6261	0.5	0.4	0.89	0.64	0.94	0.61	0.00	0.69
		1.0	0.2	0.87	0.52	0.94	0.5	0.00	1.00
AMES	6512	0.5	0.4	0.82	0.86	0.75	0.62	0.00	0.79
		1.0	0.2	0.79	0.82	0.75	0.57	0.00	1.00
MRTD[e]	1184	0.6	0.2	0.00	0.00	0.00	0.00	0.79	0.69
		1.0	0.2	0.00	0.00	0.00	0.00	0.74	1.00

[a]Number of compounds in the dataset; [b]Tanimoto-distance threshold value; [c]Smoothing factor; [d]Pearson's correlation coefficient ; [e]Regression model.

Table 3: Molecular and Biological properties of Cuminaldehyde

originalSMILES O=CC1CCC(CC1)C(C)C miSMILES: O=CC1CCC(CC1)C(C)C 4-(Propan-2-yl)cyclohexane-1-carbaldehyde	Molecular Properties	Calculated Values
	miLogP	3.24
	TPSA	17.07
	Natoms	11
	MW	148.21
	nON	1
	nOHNH	0
	Nviolations	0
	Nrotb	2
	volume	152.98
	Biological Properties	Bioactivity Scores
	GPCR ligand	-1.15
	Ion channel modulator	-0.44
	Kinase inhibitor	-1.22
	Nuclear receptor ligand	-0.86
	Protease inhibitor	-1.48
	Enzyme inhibitor	-0.64

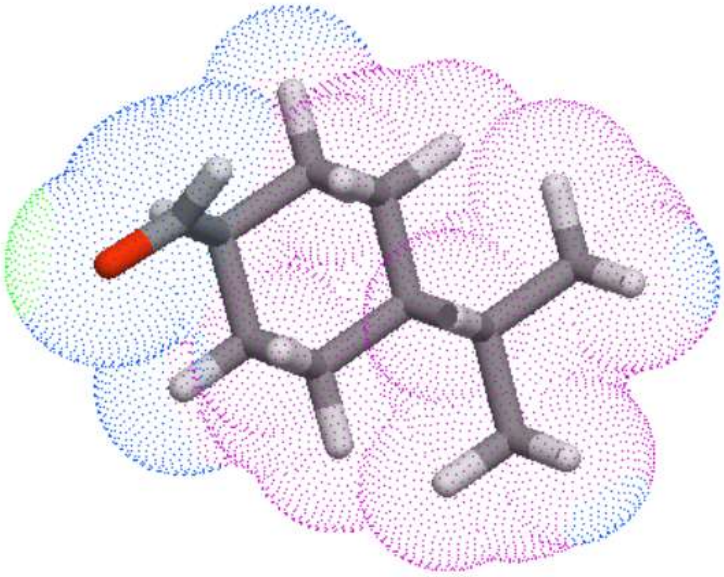

Figure 1: 3D Structure of Cuminaldehyde

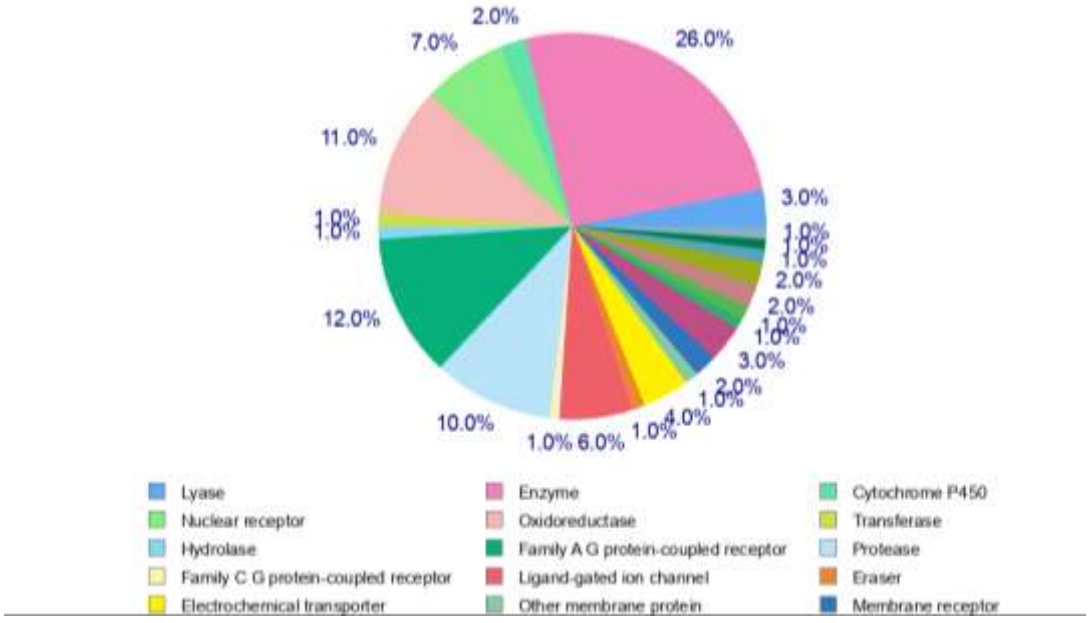

Figure 2: Predicted Bioactivity Target Chart for Cuminaldehyde

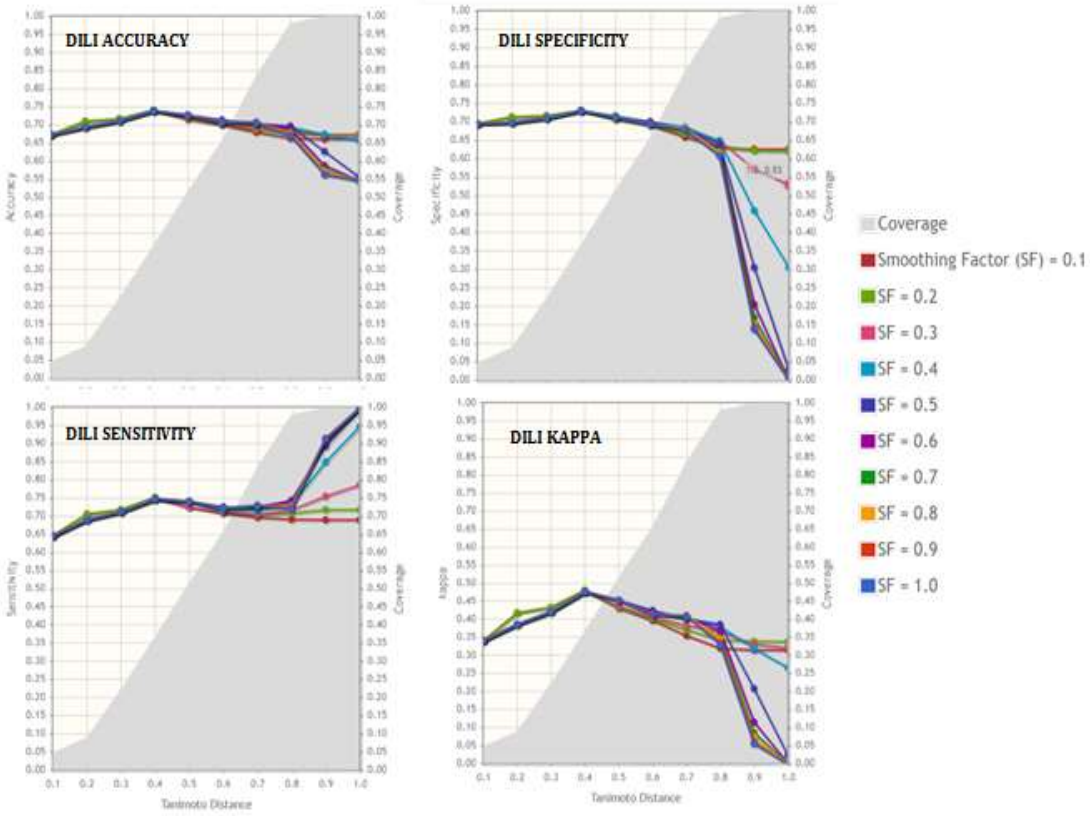

Figure 3a: Accuracy, specificity, sensitivity and kappa measure of DILI induced by CA

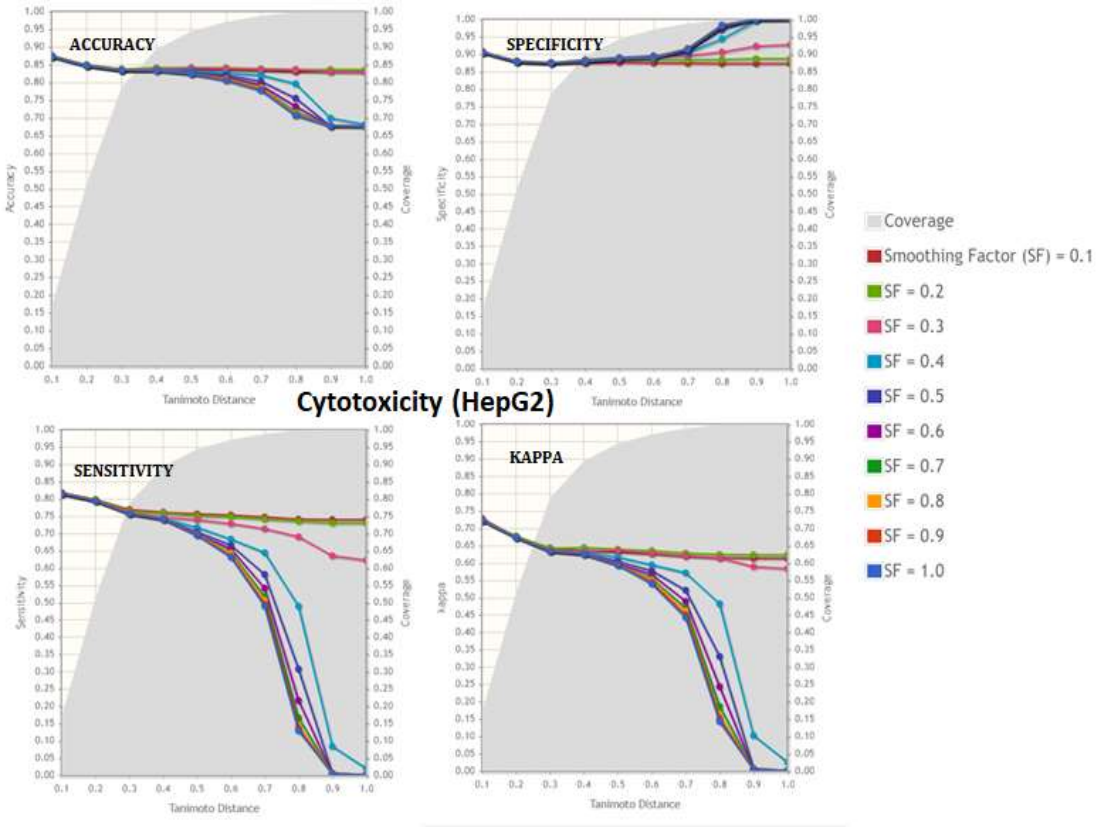

Figure 3b: Accuracy, specificity, sensitivity and kappa measure of Cytotoxicity (HepG2) induced by CA

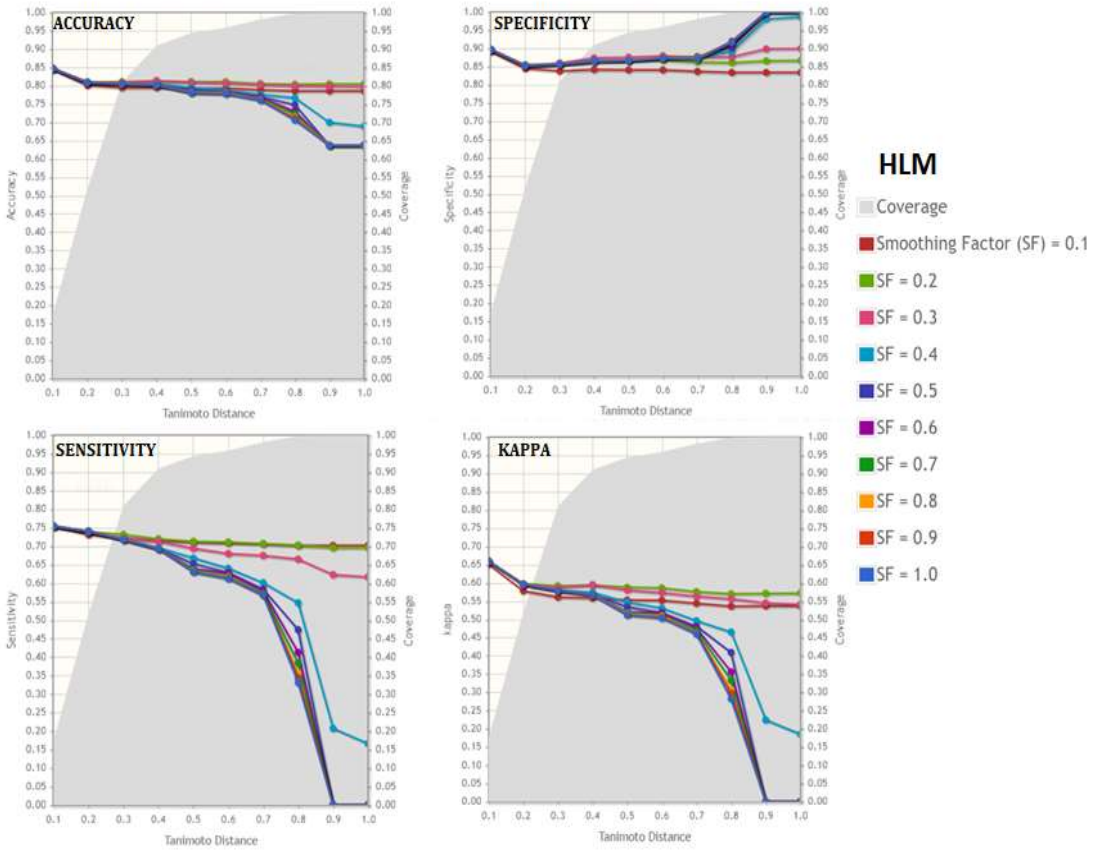

Figure 3c: Accuracy, specificity, sensitivity and kappa measure of Metabolism HLM induced by CA

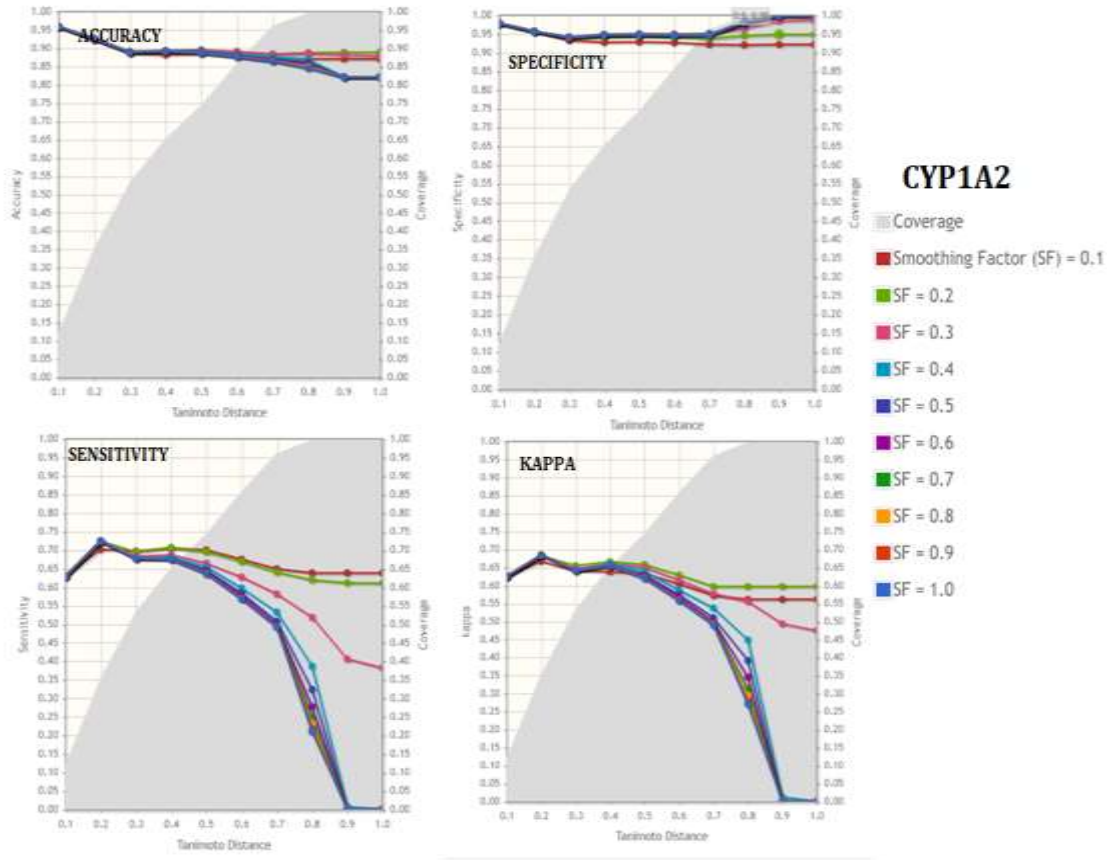

Figure 3d: Accuracy, specificity, sensitivity and kappa measure of CYP inhibition induced by CA

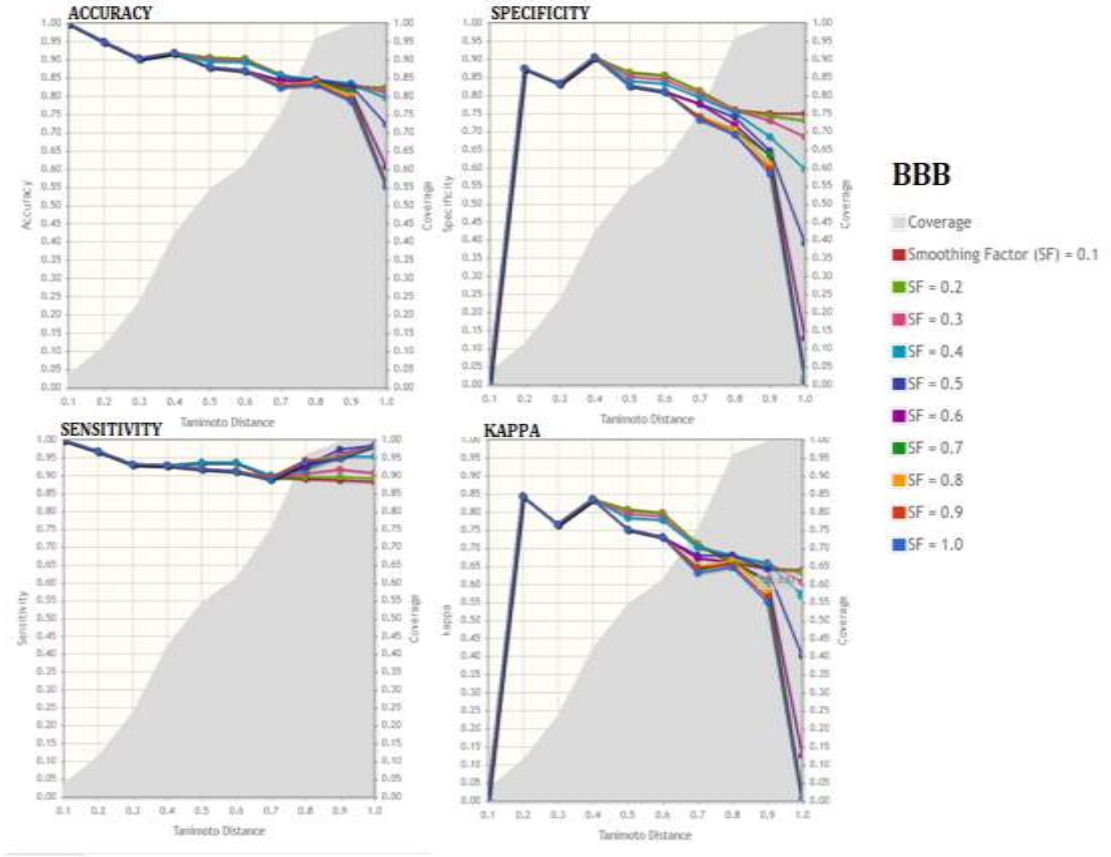

Figure 3e: Accuracy, specificity, sensitivity and kappa measure of BBB induced by CA

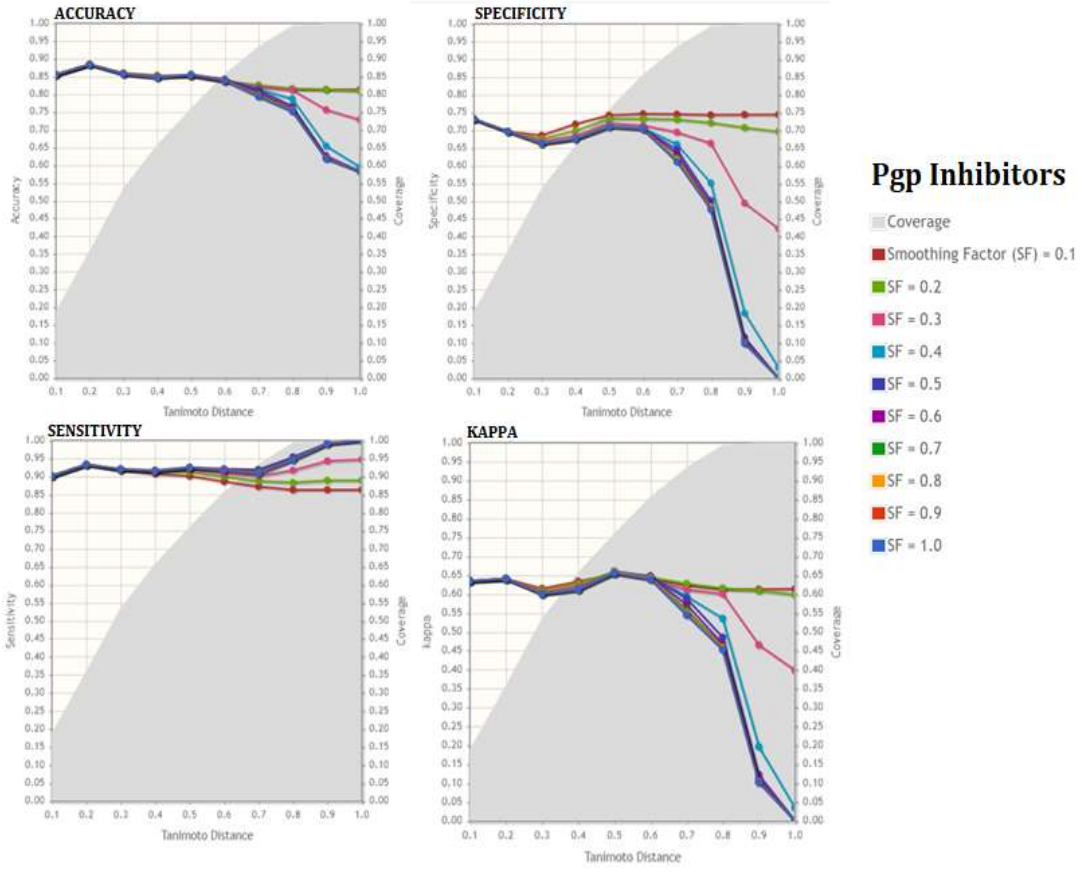

Figure 3f1: Accuracy, specificity, sensitivity and kappa measure of Pgp Inhibitors induced by CA

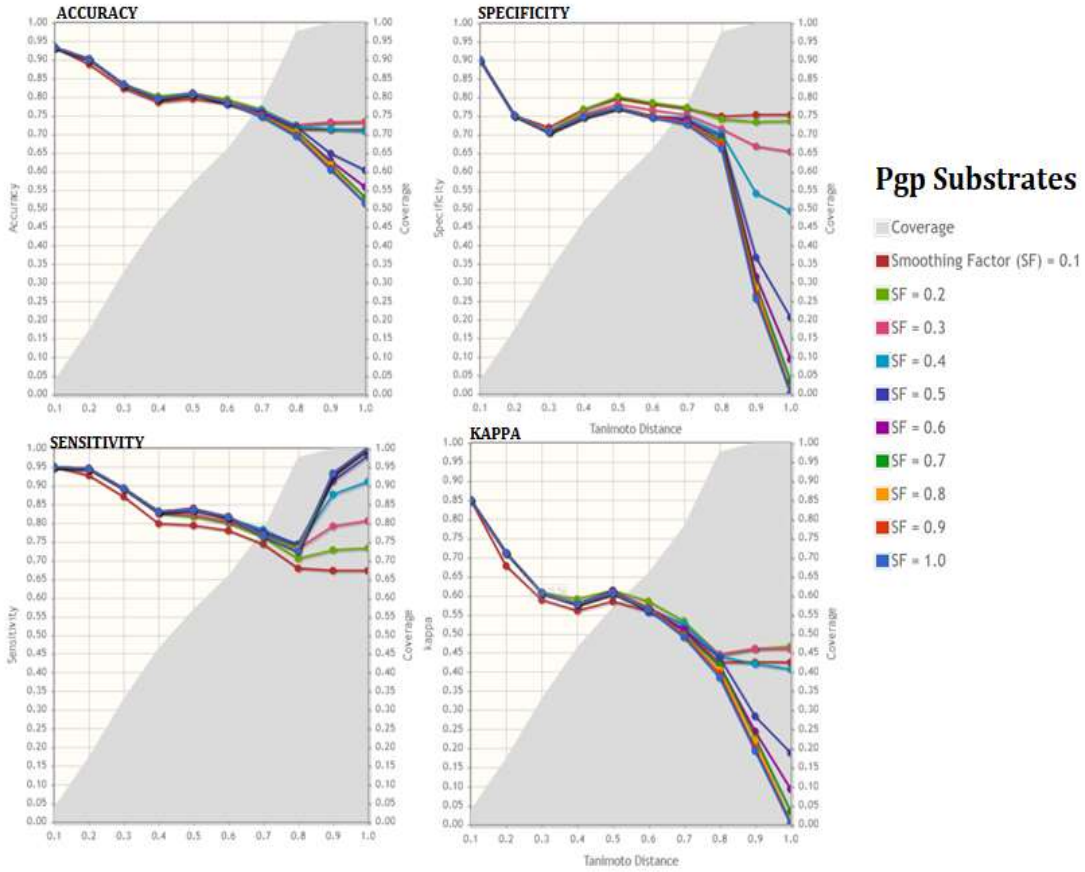

Figure 3f2: Accuracy, specificity, sensitivity and kappa measure of Pgp Substrates induced by CA

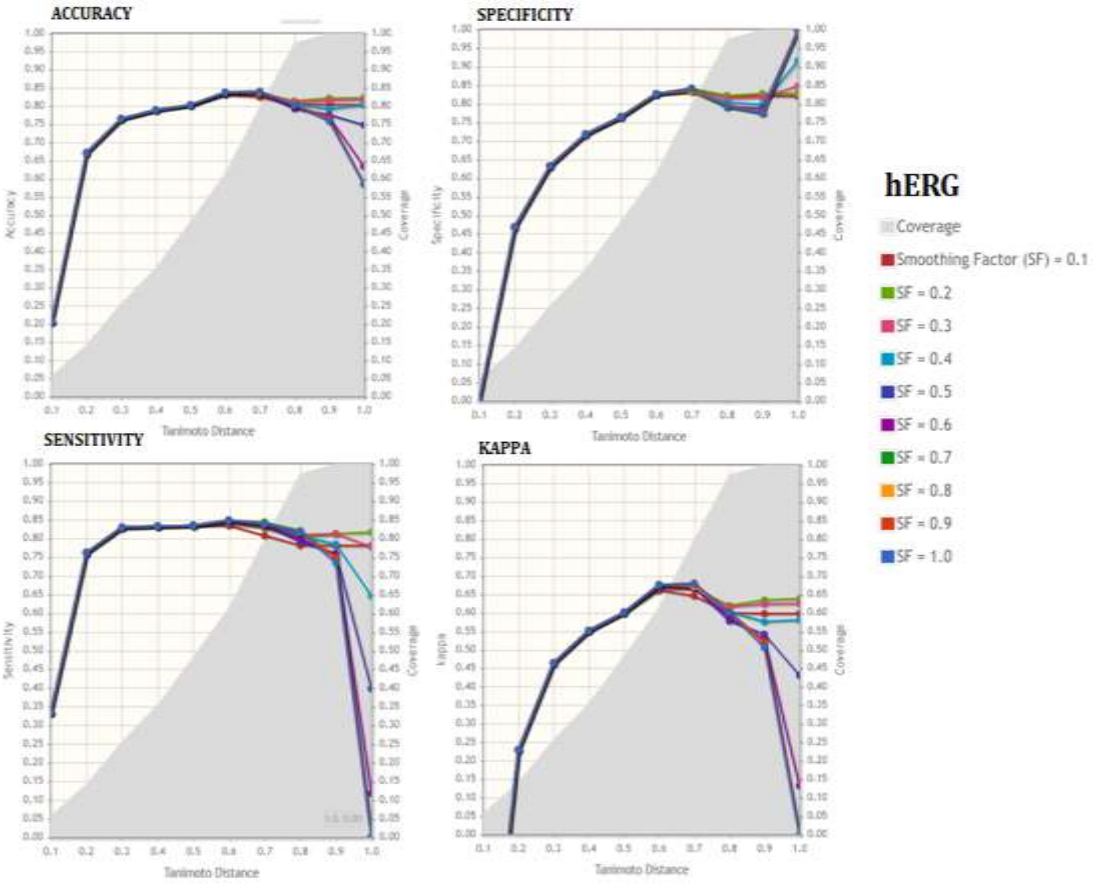

Figure 3g: Accuracy, specificity, sensitivity and kappa measure of hERG (Cardiotoxicity) induced by CA

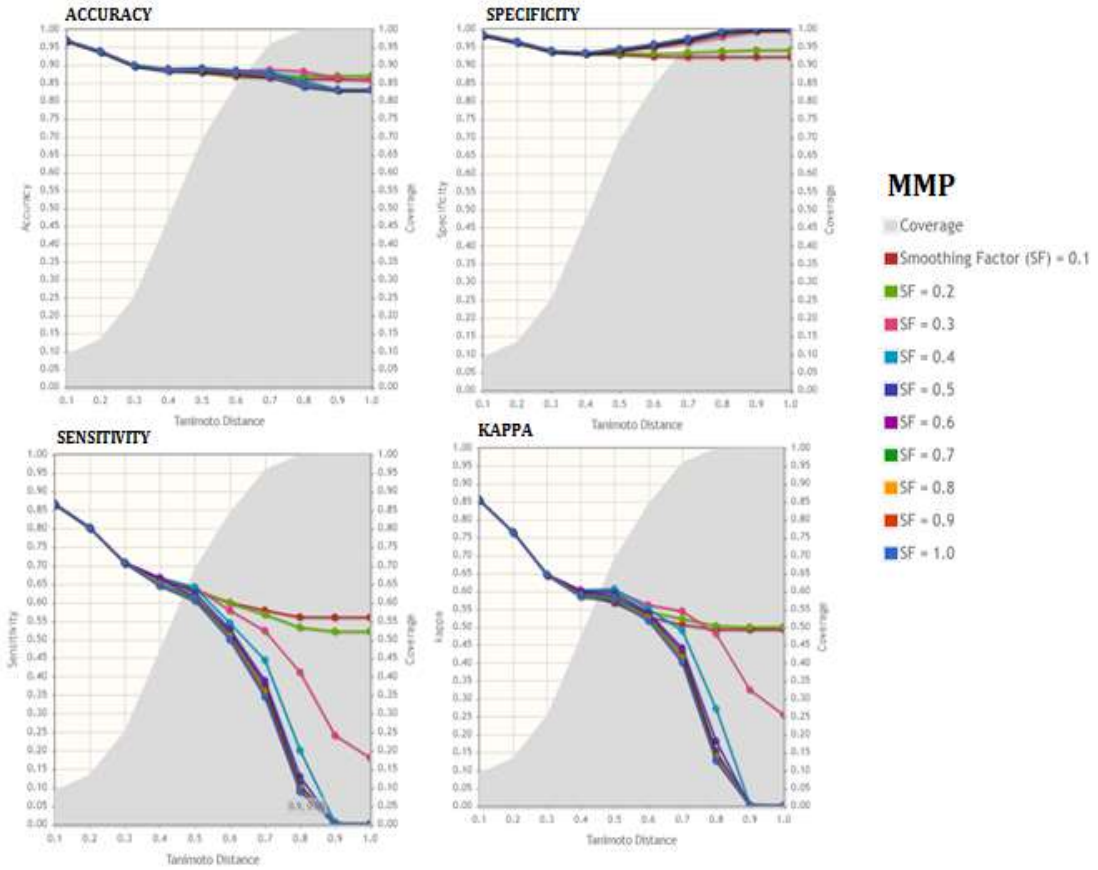

Figure 3h: Accuracy, specificity, sensitivity and kappa measure of MMP (Mitochondrial Toxicity) induced by CA

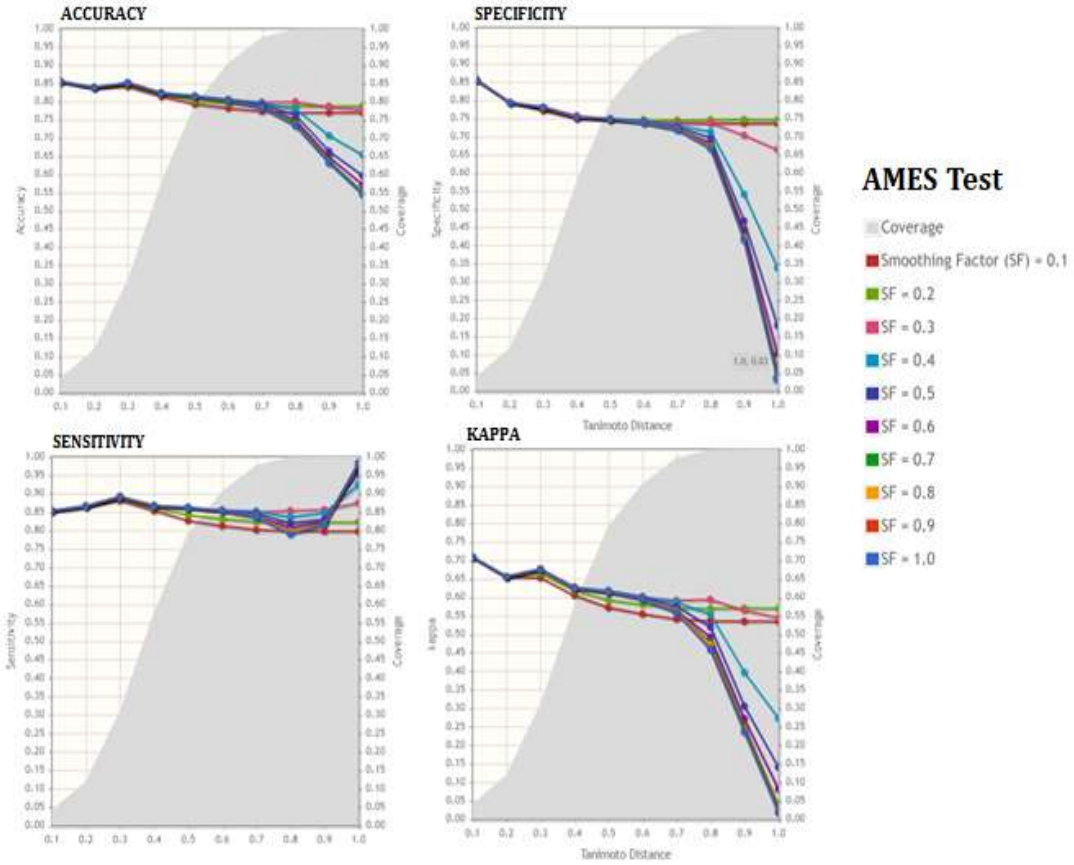

Figure 3i: Accuracy, specificity, sensitivity and kappa measure of Mutagenicity (Ames test) induced by CA

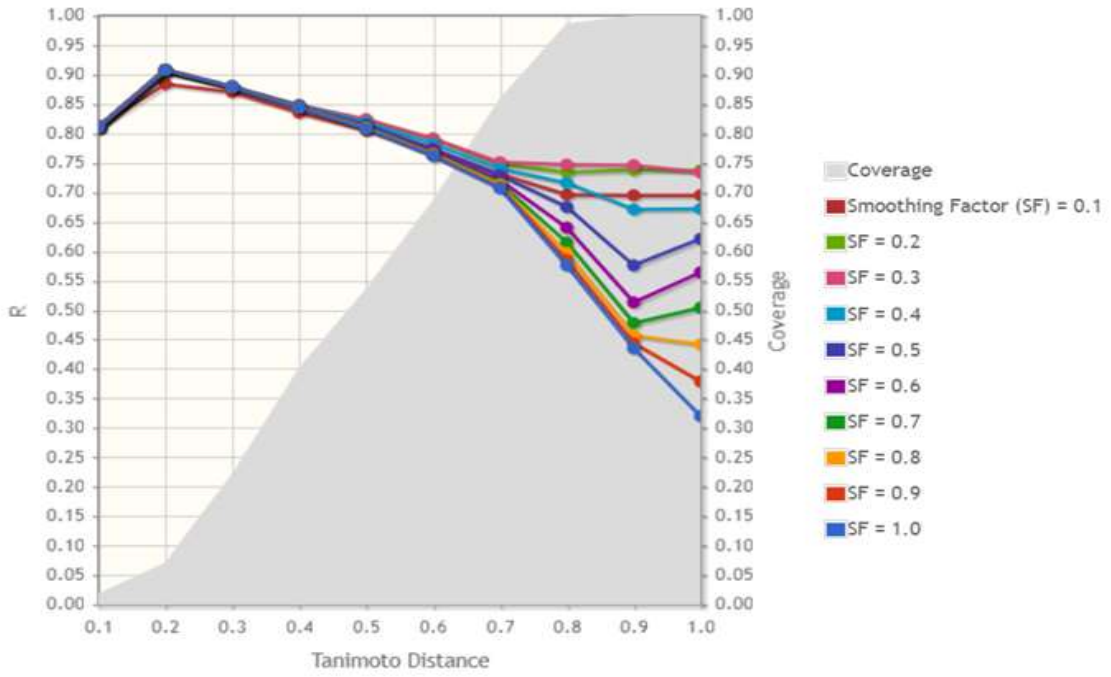

Figure 3j: Accuracy, specificity, sensitivity and kappa measure of MRTD induced by CA