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Original Article

COMPARISON OF PARTITION COEFFICIENT (LOG P) OF DRUGS: COMPUTATIONAL AND EXPERIMENTAL DATA STUDY

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ABSTRACT

Objective: The objective of this study was to determine the accuracy of the Log P calculation program (*OSIRIS*®, SCF bio®, Molinspiration®, ALOGPS 2.1®, Molsoft®, ACD/logP ®, PkCSM ®, and Swiss ADME ®) comparing it with the Log P value from the experimental results of the partition coefficient between n-octanol-water (Log P exp) taken from journals and databases.

Methods: The predicted results of the computational Log P as the independent variable and the experimental Log P as the dependent variable then the data were analyzed statistically with the SPSS program to find the best correlation.

Results: In this study, the result shows that the applications that have the best correlation with the experimental Log P are ACDlogP, MolLogP, and ALOGPS, with successive results of the R square are 0.928, 0.921, and 0.907, respectively. The results of this correlation are expressed by positive results and high-degree correlations are obtained.

Conclusion: This result suggests that the Log P calculation program (ACDlogP, MolLogP, and ALOGPS) has a good correlation with the experimental Log P value in determining the lipophilicity of the compound.

Keywords: Partition coefficient, Log P, Drug, Computational study, Experimental study, Statistical analysis

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INTRODUCTION

The partition coefficient is the ratio of the equilibrium concentrations of a compound in two immiscible solvents, non-polar and polar. They are typically reported as the logarithm of this concentration ratio (log P) [1]. The log P value describes the lipophilicity of a drug and is an indication of its ability to cross the cell membrane [2]. Lipophilicity affects the formation of new drug compounds and also plays a major role in regulating the kinetic and dynamic aspects of drug action [3]. The factor that determines the physical and chemical properties of the lipophilicity of drug compounds is the interaction between the solute and solvent molecules. In the design of the new drug, physicochemical properties help to determine the ability of the drug to penetrate lipids and reach its receptors [4]. The greater the partition coefficient, the higher the solubility in lipid and vice versa, it can be stated that the greater lipophilicity of the compound, the more non-polar it will be [5].

Determination of the partition coefficient experimentally is carried out by distributing a certain amount of a drug compound into an equilibrium system between two phases, namely polar solvents and non-polar solvents and the commonly used solvents are n-octanol and water [6]. This experimental determination is relatively expensive because it requires costs for organic solvents and analysis, needs more time for taking the experiment, and also resulting organic waste [7].

Currently, there are many programs used to calculate the Log P value that have been developed to make it easier and faster, including determining the Log P value of a drug compound using the computational study [8-11]. The computational study is often used to determine the structure of compounds and physicochemical properties of drug compounds easily and quickly by studying the properties of molecules and interactions between molecules. Determination of Log p-value by computation is supported by software that is available commercially or available on the web and can be accessed free of charge. This offers advantages in terms of time and cost. This software can predict the Log P value of a compound; however, no research discusses the accuracy of this software in determining the Log P value.

This study aims to determine the accuracy of the Log P calculation program; there are *OSIRIS*®, SCF bio®, Molinspiration®, ALOGPS 2.1®, Molsoft®, ACD/logP ®, PkCSM ®, and Swiss ADME ®, then compare it with the Log P value from the experimental results. The Log P value of the experimental result was obtained from the article and database that have determined the Log P value experimentally. The data was obtained then analyzed statistically with the SPSS program.

MATERIALS AND METHODS

Drug test compound

In this study, 50 drug compound was used as test compound. These compounds are chosen following Lipinski's Rule of Five and the data availability of Log P value experimentally from databases or published journals. The compounds are acetaminophen, alprazolam, alprenolol, amphetamine, amobarbital, clofibric acid, betamethasone, bromazepam, cimetidine, clobazam, demoxepam, diazepam, diphenhydramine, disopyramide, droperidol, flurbiprofen, furosemide, ibuprofen, imipramine, indomethacin, caffeine, captropyl, ketoprene, chloramphenicol, codeine, corticosterone, chlordiazepoxide, lidocain, mebendazole, methamphetamine, metronidazole, nifedipine, nitrazepam, oxazepam, phenytoin, pindolol, prednisolone, prednisone, progesterone, propranolol, pseudoephedrin, quinidine, simvastatin, spironolactone, sulfadiazine, sulfamethoxazole, sulfanilamide, tetracycline, tetrazepam, verapamil. The SMILES code of the 2D and 3D structures of these compounds is taken from PubChem (http://pubchem.ncbi.nlm.nih.gov) [60].

Computational method

Prediction of the Log P value on application programs and websites is carried out by following Lipinski's Rule of Five, that the molecular weight is <500 Da, the Log P value is<5, the number of hydrogen bond donors is<5, and the number of hydrogen bond acceptors is<10 [61]. The application program used in this study were *OSIRIS*®,

SCF bio®, Molinspiration®, ALOGPS 2.1®, Molsoft®, ACD/logP ®, PkCSM ®, and Swiss ADME ®.

OSIRIS®

The OSIRIS Property Explorer or CLogP open-source software program (https://www.organic-chemistry.org/prog/peo/) is used to predict the drug similarity of drug compounds by involving commercially available drug databases. This program can predict several important drug candidate parameters, one of which is the Log P value, the overall drug score is estimated by combining results of (cLog P), Molecular Weight, risk of toxicity, and drug similarity. In the determining Log P value with OSIRIS, the SMILES code of the drug compound was input into this application, and parameters like cLogP value, solubility, molecular weight, similarity, and drug score will obtain [62].

SCF bio®

SCFbio (Supercomputing Facility for Bioinformatics and Computational Biology) is free software that can be opened on the Lipinski Rule of Five websites (http://scfbio-iitd.res.in) to predict compounds with drug-like properties based on the physicochemistry parameter of the compounds. The parameters include Lipinski's rule of 5 [63]. In the determining Log P value with SCFbio, the drug structure should be prepared in *. Pdb format and then upload it to the software.

Molinspiration®

Molinspiration or MiLogP is used to calculate various molecular properties and predict drug compounds. Molecular properties such as the partition coefficient (Log P), in Lipinski's rule of five, are calculated to evaluate the drug similarity of the compounds. These results are obtained from the Log P value that has been calculated experimentally, namely from a training set of more than twelve thousand on a free online site (https://molinspiration.com/cgi-bin/properties) where the partition coefficient value is miLogP [64]. SMILES code of the drug structure must be input to the sites to get the Log P value.

ALOGPS 2.1®

The ALOGPS program for calculating Log P was developed to predict the partition coefficient of 1-octanol/water (Log P) and the solubility of neutral compounds in water with a free Java-based online site (http://vcclab.org/lab/alogps/). This method was developed based on the analysis of neutral tissue ensembles of 12908 organic compounds. Some parameters combine several indices of atomic type or bond type with similar physicochemical properties [65]. To get the Log P value with this software, the drug structure must be prepared in the format SDF/MOL2/SMILES code.

Molsoft®

Molsoft or molecules *in silico* is software that can be opened for free on the website (http://www.molsoft.com/mprop/), which is commonly used to predict the drug-likeness of a molecular structure, including the prediction of a Log P value [66]. SMILES code of the drug structure must be input to the sites to get the Log P value.

ACD/logP ®

Advanced Chemistry Development (ACD/labs) is software used to develop an analytical, chemical, and biological understanding of organic compounds with a series of predictive tools and evaluate various molecular properties, including LogP based on chemical structure. The software can be accessed at https://www.acdlabs.com/products/percepta-platform/physchem-suite/ [67]. To use this software, drug structure can be uploaded or drawn first in the ChemSketch in their software.

PkCSM ®

PkCSM ® (predicting small-molecule pharmacokinetic properties using graph-based signatures) is an online application to predict pharmacokinetic properties and toxicity, including ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) for drug development. The performance of the pkCSM software can also determine the partition coefficient value (Log P) of a drug with the web on the site (http://biosig.unimelb.edu.au/pkcsm/prediction) [68]. SMILES code of the drug structure must be input to the sites to get the Log P value.

Swiss ADME ®

SwissADME is a free web tool for evaluating the pharmacokinetic properties and drug-likeness of small molecules freely accessible at http://www.swissadme.ch. This tool can also be used to determine parameters such as physicochemical properties, lipophilicity, and Log p values [69]. SMILES code of the drug structure must be input to get the Log P value.

Determination of partition coefficient correlation

Correlation of the partition coefficient of a drug compound was performed using the SPSS for Windows program using correlation analysis and simple linear regression. In this study, the relationship between the dependent variable and the independent variable was carried out by analyzing the data collected, the relationship between the predicted Log P as the independent variable, and the experimental Log P as the dependent variable.

RESULTS AND DISCUSSION

Experimentally log P data of compound

Experimentally Log P data of the compound was obtained from databases or published journals. The result of the experimental Log P data is shown in table 1. Each compound has a different Log P value depending on the structure of the compound. The Log P value obtained varies from-1.30 to 4.77. The log P value describes the lipophilicity of a drug, the greater the log P value, the higher the solubility in lipids and the more non-polar compound it will be [5]. For example, acetaminophen and simvastatin have log P value 0.46 and 4.68, respectively. It show that simvastatin is more lipophilic that acetaminophen.

Table 1: Data of experimental Log P

No	Drug compound	Log P	Ref.	No	Drug compound	Log P	Ref.
1	Acetaminophen	0.46	[12]	26	Corticosterone	1.94	[13]
2	Alprazolam	2.12	[14]	27	*Chlordiazepoxide*	2.44	[15]
3	Alprenolol	3.10	[7]	28	Lidocaine	2.26	[16]
4	Amphetamine	1.76	[17]	29	Mebendazole	2.83	[18]
5	Amobarbital	2.07	[19]	30	Metamphetamine	2.07	[20]
6	Clofibric acid	3.30	[21]	31	Metronidazole	-0.02	[22]
7	Betamethasone	1.83	[23]	32	Nifedipine	2.20	[24]
8	Bromazepam	2.05	[25]	33	Nitrazepam	2.25	[26]
9	Cimetidine	0.40	[27]	34	Oxazepam	2.24	[28]
10	Clobazam	2.12	[29]	35	Phenytoin	2.47	[30]
11	Demoxepam	1.49	[31]	36	Pindolol	1.75	[32]
12	Diazepam	2.82	[14]	37	Prednisolone	1.62	[33]
13	Diphenhydramine	3.27	[34]	38	prednisone	1.46	[35]
14	Disopyramide	2.58	[36]	39	Progesterone	3.87	[37]
15	Droperidol	3.50	[38]	40	Propranolol	3.48	[39]

No	Drug compound	Log P	Ref.	No	Drug compound	Log P	Ref.
16	Flurbiprofen	4.16	[40]	41	Pseudoephedrine	0.89	[41]
17	Furosemide	2.03	[42]	42	Quinidine	3.44	[43]
18	Ibuprofen	3.97	[44]	43	Simvastatin	4.68	[45]
19	Imipramine	4.77	[46]	44	Spironolactone	2.78	[47]
20	Indomethacin	4.27	[48]	45	Sulfadiazine	-0.09	[49]
21	Caffeine	-0.07	[50]	46	Sulfamethoxazole	0.89	[51]
22	Captopril	0.34	[52]	47	Sulfanilamide	-0.62	[53]
23	Ketoprofen	3.12	[44]	48	Tetracycline	-1.30	[54]
24	Chloramphenicol	1.14	[55]	49	Tetrazepam	3.20	[56]
25	Codeine	1.19	[57]	50	Verapamil	3.79	[58]

Correlation study of Log P based on computational prediction and experimental

The experimental value of the n-octanol/water partition coefficients (LogP exp.) with the calculation partition coefficients (Log P from software) for the studied drugs were compared. The log P value of each compound was determined computationally using different software including *OSIRIS*®, SCF bio®, Molinspiration®, ALOGPS 2.1®, Molsoft®, ACD/logP ®, PkCSM ®, and Swiss ADME ®. The result of the prediction of the Log P value of fifty compounds was shown in table 2. The correlation between the Log P value from the computational software program and the experimental was then statistically analyzed.

Table 2: Data prediction of Log P value based on computational running

No	Drug compound	LogP Exp.	ClogP	SCFbio	MiLogP	Alogps	molLogP	ACD Logp	pkCSM	SwissADME
1	Acetaminophen	0.46	1.02	1.35	0.68	0.51	0.79	0.34	1.35	0.93
2	Alprazolam	2.12	2.62	3.49	2.29	2.23	2.06	2.50	3.58	2.50
3	Alprenolol	3.10	2.25	2.15	2.58	2.59	2.94	2.88	2.15	2.13
4	Amphetamine	1.76	1.45	1.57	1.32	1.85	1.79	1.81	1.57	1.91
5	Amobarbital	2.07	1.30	1.18	1.78	1.87	2.02	2.05	1.18	1.03
6	Clofibric acid	3.30	2.90	3.06	3.72	3.99	3.52	3.32	3.06	3.02
7	Betamethasone	1.83	1.29	1.89	2.06	1.93	2.07	1.87	1.89	2.14
8	Bromazepam	2.05	1.80	2.63	2.41	2.09	2.08	1.65	2.63	2.18
9	Cimetidine	0.40	0.17	0.59	0.14	0.44	0.18	0.07	0.59	0.63
10	Clobazam	2.12	2.89	3.37	2.55	2.14	2.11	1.69	3.37	2.01
11	Demoxepam	1.49	1.32	1.89	3.13	2.50	2.71	1.23	1.34	2.48
12	Diazepam	2.82	2.98	2.89	2.74	2.63	2.86	2.91	3.15	2.44
13	Diphenhydramine	3.27	2.91	3.35	3.50	3.44	3.40	3.66	3.35	2.58
14	Disopyramide	2.58	2.21	3.36	2.78	3.21	2.64	2.86	3.36	3.00
15	Droperidol	3.50	3.46	4.43	3.40	3.93	3.46	3.51	3.67	3.06
16	Flurbiprofen	4.16	3.33	3.68	4.05	3.57	3.98	4.12	3.68	3.18
17	Furosemide	2.03	0.77	2.97	1.77	2.71	2.10	3.10	1.89	0.86
18	Ibuprofen	3.97	3.00	3.07	3.46	3.50	3.85	3.72	3.07	2.57
19	Imipramine	4.77	3.89	3.87	4.16	4.53	4.83	4.80	3.87	3.80
20	Indomethacin	4.27	4.00	3.92	3.99	4.25	4.00	3.10	3.92	3.08
21	Caffeine	-0.07	-0.18	0.06	0.06	-0.24	-0.08	-0.13	-1.02	-0.28
22	Captopril	0.34	0.37	0.62	-1.09	1.02	0.41	0.27	0.62	0.62
23	Ketoprofen	3.12	2.70	3.10	3.59	3.29	3.19	2.81	3.10	2.84
24	Chloramphenicol	1.14	-0.42	0.90	0.73	1.15	-0.16	1.02	0.90	0.30
25	Codeine	1.19	1.12	1.75	1.41	1.20	1.10	1.20	1.50	1.80
26	Corticosterone	1.94	2.24	2.66	1.88	2.09	1.59	1.76	2.66	2.41
27	*Chlordiazepoxide*	2.44	1.45	3.03	3.73	2.98	3.05	1.82	1.84	2.66
28	Lidocaine	2.26	2.16	3.00	2.13	1.81	2.55	2.36	3.00	2.31
29	Mebendazole	2.83	2.67	2.97	2.89	2.95	3.13	2.83	2.97	2.30
30	Metamphetamine	2.07	1.81	1.83	2.23	2.23	2.21	1.94	1.83	1.75
31	Metronidazole	-0.02	-1.05	0.09	-0.47	-0.15	-0.95	-0.01	-0.09	-0.47
32	Nifedipine	2.20	1.55	2.17	3.07	2.49	1.51	2.97	2.17	1.07
33	Nitrazepam	2.25	1.10	2.38	2.14	1.95	1.10	2.18	2.38	1.50
34	Oxazepam	2.24	2.28	2.44	1.84	2.01	2.01	2.31	2.44	2.28
35	Phenytoin	2.47	1.67	1.76	2.18	2.26	2.31	2.52	1.76	1.56
36	Pindolol	1.75	1.26	1.90	1.98	2.17	1.97	1.97	1.90	1.42
37	Prednisolone	1.62	1.14	1.55	1.59	1.66	1.89	1.49	1.55	1.31
38	prednisone	1.46	1.29	1.76	1.41	2.07	1.72	1.57	1.76	1.42
39	Progesterone	3.87	4.02	4.72	3.81	3.58	3.52	4.04	4.72	4.03
40	Propranolol	3.48	2.42	2.57	2.97	3.03	3.42	3.10	2.57	2.84
41	Pseudoephedrine	0.89	0.74	1.32	1.24	1.00	1.15	1.05	1.32	1.46
42	Quinidine	3.44	2.61	3.17	3.06	2.82	3.21	3.44	3.17	2.81
43	Simvastatin	4.68	4.46	4.58	4.76	4.51	4.80	4.42	4.58	3.36
44	Spironolactone	2.78	3.21	4.85	3.03	3.10	2.40	3.12	4.85	3.77
45	Sulfadiazine	-0.09	0.09	1.94	-0.04	0.25	-0.30	-0.12	0.85	0.24
46	Sulfamethoxazole	0.89	0.44	2.44	0.61	0.79	0.90	0.89	1.36	0.71
47	Sulfanilamide	-0.62	-0.25	0.99	-0.29	-0.16	-0.53	-0.72	-0.08	-0.01
48	Tetracycline	-1.30	-1.26	-0.60	-0.24	-0.73	-1.44	-0.07	-0.37	-0.58
49	Tetrazepam	3.20	2.88	3.34	3.84	3.53	3.24	2.88	3.60	2.62
50	Verapamil	3.79	4.93	5.09	4.55	5.23	3.87	3.90	5.09	4.45

OSIRIS®

The result of determining of partition coefficient using OSIRIS is the ClogP value. The correlation between the ClogP value and the experimental LogP value is shown in fig. 1. Based on the statistical data, the Pearson correlation value is 0.924, which means that a high degree correlation is obtained [59] with the R square being 0.853. The R square describes how well the predicted value match the observed value. The result of the R square value shows that the ClogP and the experimental Log P are correlated with a percentage of 85.3%. This means that the regression model explains 85.3% of the data is fitted with the observed data values. The high R square value suggests a better fit for the model.

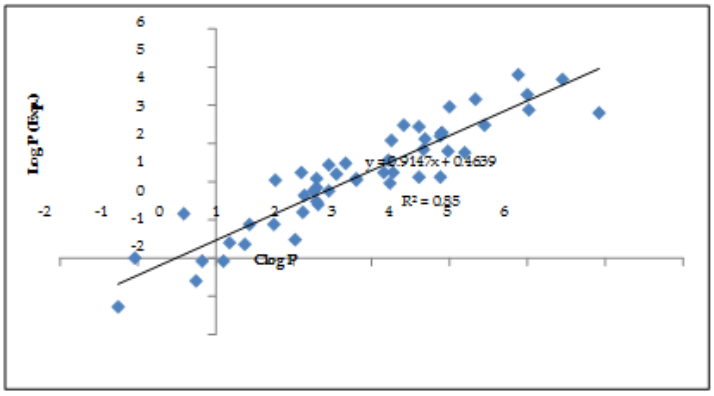

Fig. 1: Correlation of ClogP and experimental LogP

SCF bio®

The correlation between the LogP value from SCF bio and the experimental LogP value is shown in fig. 2. Based on the statistical data, the Pearson correlation value is 0.849, which means that the high degree correlation is obtained [59] and the R square was 0.722. The result of the R square value shows that the LogP value from SCF bio and the experimental Log P is correlated with a percentage of 72.2%.

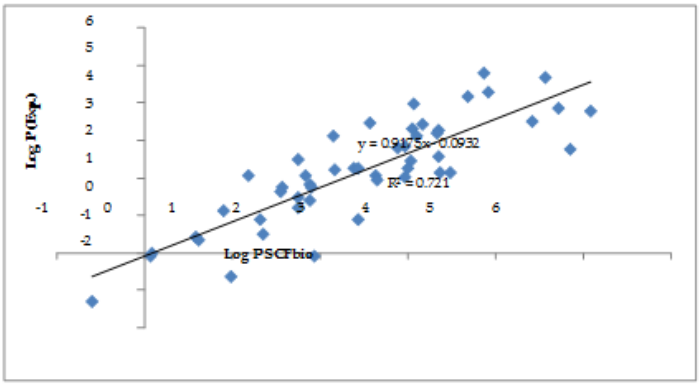

Fig. 2: Correlation of LogP from SCFbio and experimental LogP

Molinspiration®

The result of determining of partition coefficient using Molinspiration is the miLogP value. The correlation between the miLogP value and the experimental LogP value is shown in fig. 3. Based on the statistical data, the Pearson correlation value is 0.931, which means that the high degree correlation is obtained [59] and the R square was 0.868. The result of the R square value shows that the miLogP value and the experimental Log P are correlated with a percentage of 86.8%.

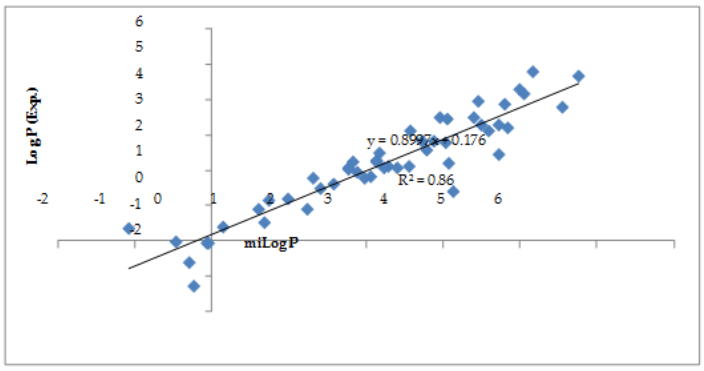

Fig. 3: Correlation of miLogP from SCFbio and experimental LogP

ALOGPS 2.1®

The correlation between the LogP value from ALOGPS and the experimental LogP value is shown in fig. 4. Based on the statistical data, the Pearson correlation value is 0.935, which means that a high degree correlation is obtained [59] and the R square was 0.907. The result of the R square value describes that the LogP value from ALOGPS and the experimental Log P is correlated with a percentage of 90.7%.

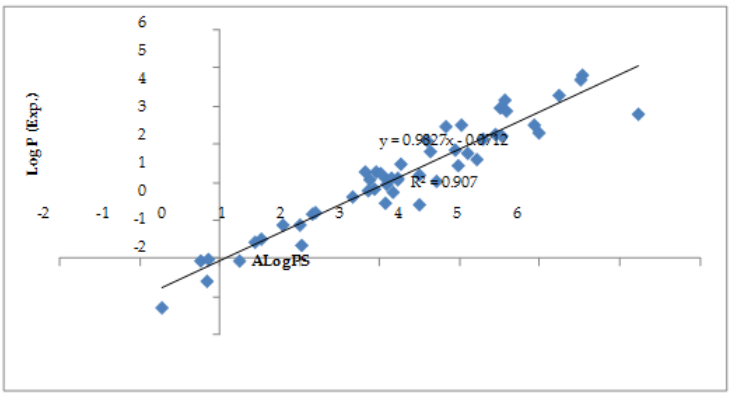

Fig. 4: Correlation of LogP from ALOGPS and experimental LogP

Molsoft®

The result of determining of partition coefficient using Molsoft is the MolLogP value. The correlation between the MolLogP value and the experimental LogP value is shown in fig. 5. Based on the statistical data, the Pearson correlation value is 0.961, which means that the high degree correlation is obtained [59] and the R square was 0.921. The result of the R square value describes that the MolLogP value and the experimental Log P are correlated with a percentage of 92.1%.

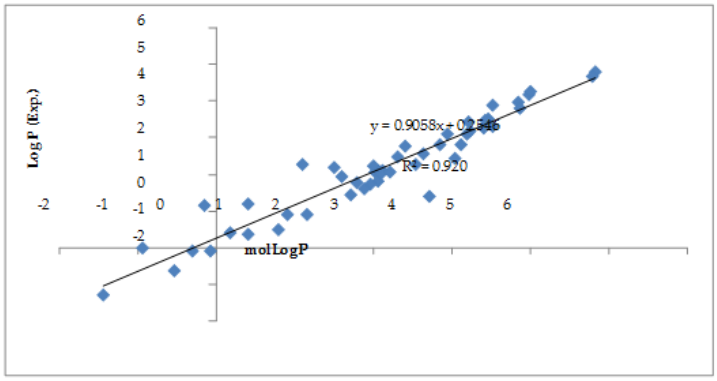

Fig. 5: Correlation of MolLogP from Molsoft and experimental LogP

ACD/logP®

The correlation of the LogP value from ACD/logP and the experimental LogP value is shown in fig. 6. Based on the statistical data, the Pearson correlation value is 0.963, which means that a high degree correlation is obtained [59] and the R square was 0.928. The result of the R square value describes that the LogP value from ACD/logP and the experimental Log P is correlated with a percentage of 92.8%.

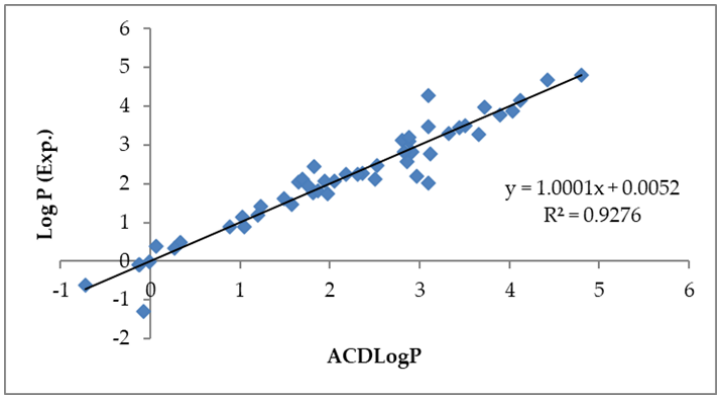

Fig. 6: Correlation of LogP from ACDLogP and experimental LogP

PkCSM®

The correlation of the LogP value from PkCSM and the experimental LogP value is shown in fig. 7. Based on the statistical data, the Pearson correlation value is 0.883 which means that the high degree correlation is obtained [59] and the R square was 0.778. The result of the R square value shows that the LogP value from ACD/logP and the experimental Log P is correlated with a percentage of 77.8%.

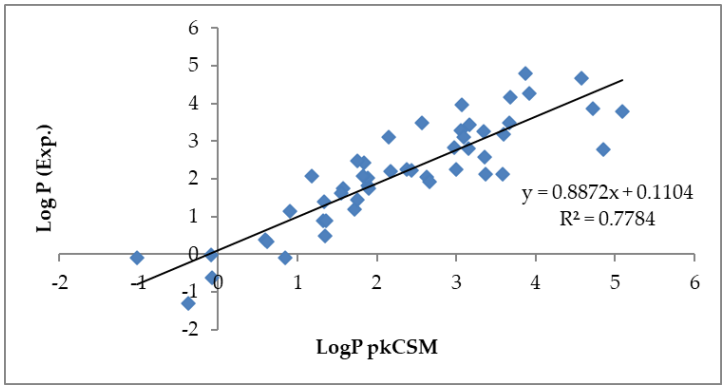

Fig. 7: Correlation of LogP from PkCSM and experimental LogP

Swiss ADME®

The correlation between the LogP value from Swiss ADME and the experimental LogP value is shown in fig. 8. Based on the statistical data, the Pearson correlation value is 0.887, which means that the high degree correlation is obtained [59] and the R square was 0.793. The result of the R square value shows that the LogP value from ACD/logP and the experimental Log P is correlated with a percentage of 79.3%.

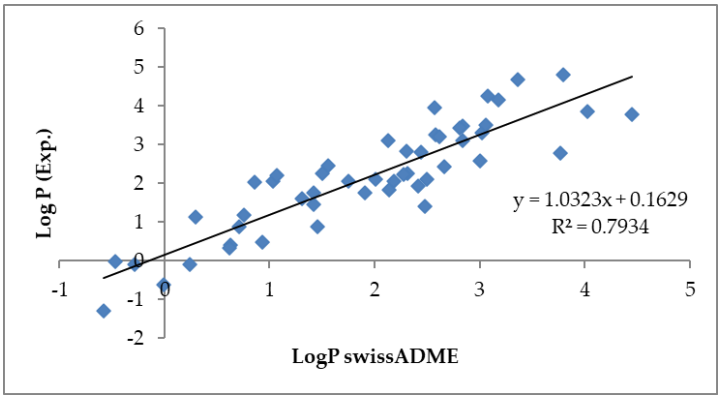

Fig. 8: Correlation of LogP from swissADME and experimental LogP

CONCLUSION

The comparative study of the determination Log P value using computational and experimental data approaches help in predicting the similarity of the Log P value of the compound based on their calculation. Determination of Log P value using a computational program offer speed and simplicity in determining the physicochemical properties of compounds. The statistical data show that ACDlogP, MolLogP, and ALOGPS computational program has the highest R square value of 92.8%, 92.1%, and 90.7%, respectively, compared to the other program. The high R square values describe a good correlation with the experimental value.

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AUTHORS CONTRIBUTIONS

All the authors contributed equally.

CONFLICT OF INTERESTS

Declared none

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