International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 114-126 www.ijprajournal.com ISSN: 2456-4494

QSAR study of monoterpenes derivative as antibacterial against Escherichia coli and Staphylococcus aureus

Anand Kumar Lakhera[1]*, Shailja Sachan[2], Shailendra Ku. Lagarkha[1].
[1]*Department of Chemistry, A.P.S. University, Rewa (M.P.) INDIA – 486003.*
[2]*Department of Chemistry, M. S. Golvalkar College, Rewa (M.P.) INDIA – 486001.*

Submitted: 25-10-2022 Accepted: 05-11-2022

ABSTRACT: The current study used QSAR (quantitative structure-activity relationship) methods to simulate the antibacterial activity of monoterpene derivatives against gram-negative Escherichia coli and gram-positive Staphylococcus aureus. Multivariate analysis produced an excellent model, which was validated using cross validation with the leave one out approach. The data set was subjected to cross-validation in order to demonstrate the prediction power of statistically significant QSAR models, which aid in the exploration of some expectedly potent compounds. The best model for predicting antibacterial activity revealed that GGI7, ATS3s, ATSC1s, SpPosA B(i), X4Av, and Chi Dz(e) are extremely useful in describing these drugs' antibacterial activities. The study found that ATS3s, GGI7, and Chi_Dz(e) contribute positively to antibacterial activity (Gram-negative E. coli and Gram-positive Staphylococcus aureus), whereas ATSC1s, SpPosA_B(i), and X4Av contribute negatively. Compounds with improved antibacterial potential can be successfully designed with a selected quantitative structure-activity relationship model.

KEYWORDS: QSAR analysis, Antibacterial activity mono terpenes, 2D QSAR, LOO, Multivariate analysis.

1. INTRODUCTION

Food-borne illness infections are an important factor for customers, the food suppliers, especially food hygiene organizations. Natural antimicrobial compounds that can suppress bacterial growth and fungus in foods have increasingly received a lot of attention in order to improve their quality and shelf life. Customers are also concerned with the safety of synthetic preservatives in food. As a result of either reaction, there appears to be a growing demand for natural compounds that can be used as various food preservatives[1, 2, 3] . The above, in turn, has led to a hunt for antimicrobials obtained from a range of natural sources. Plants, mammals, microbes, algae, and fungi are all sources of natural antimicrobials. Several plant antibacterial studies have established the value of plant-derived compounds in food applications as well as the elements that determine their usefulness.[4,5,6,7] As a result, the chemical composition of plant-derived chemicals has to be determined in terms of antibacterial activity. Polyphenols have a broad antimicrobial impact against microbial pathogens due to structural and chemical composition variations [8,9].

The bacteria E. coli and Staphylococcus aureus cause a wide range of illnesses in communities and hospitals [10]. The bacteria Escherichia coli are well-known for causing food poisoning [11,12]. Infection can cause hemolytic uremic syndrome, gastroenteritis, and, in rare cases, organ failure, particularly in children and the elderly. The bulk of infections are now connected to eating uncooked infected ground beef, consuming unpasteurized or fruit juice, or drinking contaminated water [13,14,15] . Symptomless intestinal shedding of the pathogen, bloody diarrhoea with stomach pains, nausea, and occasionally fever, haemolytic uremic syndrome, and coagulant thrombotic purpura are all symptoms of E. coli infections. The most common cause of nosocomial pathogens is S. aureus. It's a Gram-positive, round-shaped bacterium that's a common part of the body's microbiota, commonly found in the infection of the respiratory tracts of humans. Resistance strains of E. coli and S. aureus to a variety of medications have already been discovered in recent years all over the world. These would have emerged as a serious public health hazard, necessitating the development of novel antibacterial compounds.

Traditional drug discovery approaches are both costly and time-consuming, requiring the development of more efficient procedures in terms of both time and resources. The search for new active compounds involves the use of efficient and robust technologies that can search a chemical dataset for compounds with established biological

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 114-126 www.ijprajournal.com ISSN: 2456-4494

activity [16]. Considering both speed and cost effectiveness, QSAR investigations have been effectively used in the discovery and development of several medications [17]. The goal of this research is to employ these approaches to reveal the link between monoterpene chemical properties and biological activities in order to develop a model that can be used to create extremely effective antibacterials.

The goal of this research is to use the multivariate regression approach to create QSAR models and investigate the correlations between actual antibact erial activity and estimated chemical descriptors of 25 monoterpenes derivative as antibacterial against Escherichia coli and Staphylococcus aureus. In reality, we have had a lot of success using 2D autocorrelations and 2D matrix-based descriptors, connectivity indices predict diverse pharmacological molecule actions. A QSAR sequence was established using multiple linear regression (MLR) and cross-validation techniques to predict antibacterial activity in a series of monoterpenes derivatives as powerful agents against Escherichia coli and Staphylococcus aureus.

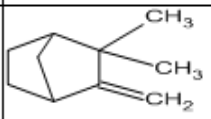
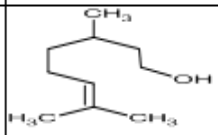
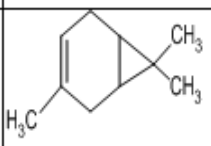
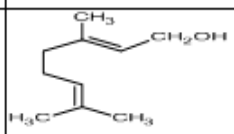
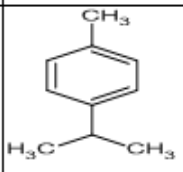
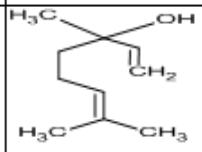
II. INHIBITORY ACTIVITY

All the monoterpenes derivatives were evaluated for their in vitro growth inhibitory activity Gram negative and Gram positive bacterial and given in the form of MIC (Minimum inhibitory concentration) which was obtained by the DMSO(Dimethyl sulfoxide) dilution method and for future QSAR analysis, the negative logarithms of pMIC=--log(MIC) were used. The inhibitory activity is directly taken from literature of Mohamed E.I.Badawy et.al. [18] And presented in Table-2.

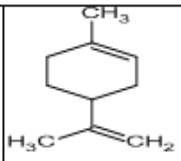
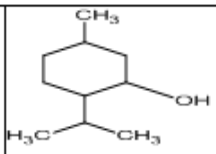
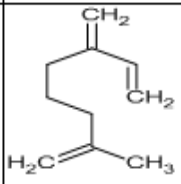
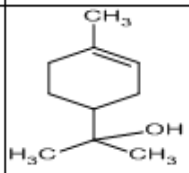
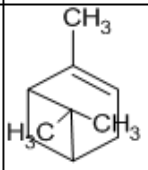
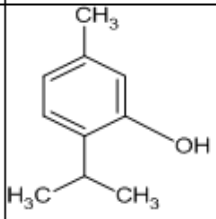
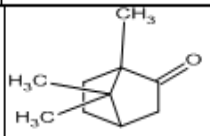
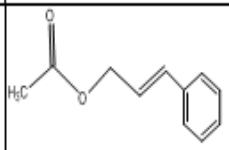
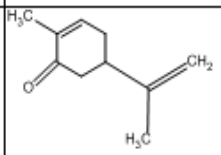
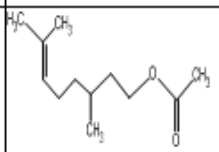
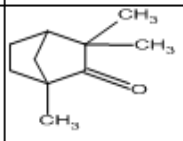
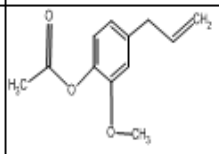
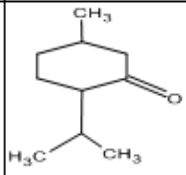
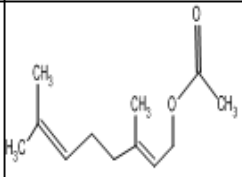
III. PRESENTATION OF DATA

In present study Table.1 represents the diff erent structure of monoterpenes derivatives and inhibitory activity against (E. coli and S. aureus) while Table-2(A&B) shows the inhibitory activity in the form of pMIC(E. coli and S. aureus) and calculated molecular descriptors and Table-3(A&B) represents the correlation matrix between descriptors and Table-4 (A&B) represent the result of regression analysis with the help of statistical descriptors while Table -5(A&B) shows cross validation statistical parameters for all developed QSAR models while in Table-6(A&B) shows the predicted, observed antibacterial activity against (E. coli and S. aureus) with residuals Figure-1(A&B) is the graph plotted between predicted and observed antibacterial activity of monoterpenes derivatives while Figure-2(A&B) shows graph plotted between the residual and observed activity and Figure – 3is the graph plotted between VIF and K.

Table-1: Structure of monoterpenes derivatives

C.No.		pMIC E. coli	pMIC S. aureus	C.No.		pMIC E. coli	pMIC S. aureus
1		2.732	2.785	14		2.13	2.398
2		2.146	2.439	15		2.398	2.477
3		2.439	2.477	16		2.114	2.423

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 114-126 www.ijprajournal.com ISSN: 2456-4494

4		2.602	2.74	17		2.439	2.602
5		1.813	2.415	18		1.74	2.352
6		2.74	2.778	19		1.653	2.13
7		2.748	2.903	20		2.724	2.829
8		2.301	2.623	21		2.591	2.653
9		2.439	2.699	22		2.699	2.813
10		1.845	2.602	23		2.602	2.778

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 114-126 www.ijprajournal.com ISSN: 2456-4494

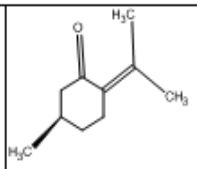
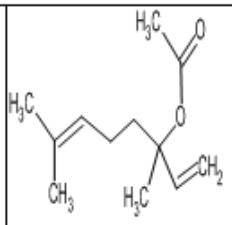
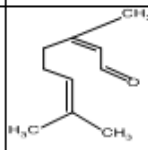
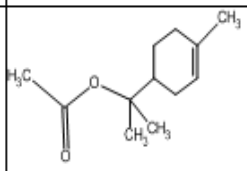
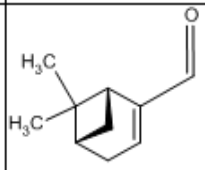
11		1.778	2.585	24		2.778	2.929
12		2.255	2.462	25		2.74	2.898
13		2.439	2.74				

Table .2: Calculated molecular descriptor for monoterpene derivatives as antibacterial agents against E. c oli and Staphylococcus aureus.

C.No.	MIC s. aureus	MIC E. coli	GGI7	ATS3s	ATSC1s	SpPosA_B(i)	X4Av	Chi_Dz(e)
1	2.7853	2.732394	0	5.064	16.814	1.288	0.031	0.637
2	2.4393	2.146128	0	4.502	16.814	1.269	0.031	0.581
3	2.4771	2.439333	0	4.601	12.944	1.301	0.031	0.555
4	2.7403	2.60206	0	4.601	12.944	1.272	0.031	0.499
5	2.4149	1.812913	0	4.506	15.278	1.29	0.031	0.364
6	2.7781	2.740363	0	4.747	16.814	1.267	0.031	0.626
7	2.903	2.748188	0	5.558	31.499	1.298	0.03	0.623
8	2.6232	2.30103	0	5.077	25.332	1.322	0.03	0.494
9	2.6989	2.439333	0	5.52	30.978	1.299	0.031	0.609
10	2.602	1.845098	0	4.835	25.332	1.277	0.03	0.459
11	2.5854	1.778151	0	4.835	25.332	1.295	0.03	0.501
12	2.4623	2.255273	0.062	4.425	19.287	1.298	0.03	0.365
13	2.7403	2.439333	0	4.858	19.554	1.293	0.031	0.578
14	2.39794	2.130334	0.062	4.425	19.287	1.254	0.03	0.334
15	2.4771	2.39794	0.062	4.425	19.287	1.273	0.03	0.358
16	2.4232	2.113943	0	4.956	28.343	1.281	0.03	0.375
17	2.602	2.439333	0	4.835	25.332	1.251	0.03	0.449
18	2.3521	1.740363	0	4.887	27.643	1.267	0.031	0.468
19	2.1303	1.653213	0	4.835	25.332	1.322	0.03	0.544
20	2.8293	2.724276	0.106	4.497	12.238	1.346	0.03	0.381
21	2.65324	2.591065	0.094	4.717	25.054	1.284	0.028	0.276
22	2.81296	2.69897	0.062	4.924	20.63	1.353	0.027	0.42
23	2.7781	2.60206	0.094	4.717	25.054	1.301	0.028	0.298
24	2.9294	2.778151	0.125	4.994	29.261	1.308	0.027	0.344
25	2.8976	2.740363	0.118	5.007	29.741	1.294	0.028	0.397

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 114-126 www.ijprajournal.com ISSN: 2456-4494

Detailed Name of Descriptors

S.No.	Name of Descriptors	Detailed Name of Descriptors
1	GGI7	Topological charge index of order 7.
2	ATS3s	Broto-Moreau autocorrelation of lag 3 (log function) weighted by I-state.
3	ATSC1s	Centred Broto-Moreau autocorrelation of lag 1 weighted by I-state.
4	SpPosA_B(i)	normalized spectral positive sum from Burden matrix weighted by ionization potential
5	X4Av	Average valence connectivity index of order 4.
6	Chi_Dz(e)	Randic-like index from Barysz matrix weighted by Sanderson electronegativity.

IV.RESULT AND DISCUSSION

QSAR study of a series of monoterpenes derivatives was performed by using dragon software. In this study, inhibitory activity ($pMIC_{E.coli}$,$pMIC_{s.aureus}$) Minimum inhibitory concentration as dependent and various 2D autocorrelations, with 2D matrix-based descriptors, Connectivity indices, taken as the independent variable and regression were established using (MLR) multiple linear regression analysis. The models were selected on the basis of its statistical significance for further study. A data set of 25 compounds that the inhibitory acti vities E. coli and Staphylococcus aureus of all 25 c ompounds gave maximum and minimum value ran ge of biological activities. Due to presence of some outliers we have done final regression analysis of 2 0 selected monoterpenes derivatives as antibacterial agents against E. coli and Staphylococcus aureus b y QSAR method.

In order to understand the experimental in hibitory data of (1-25) monoterpene derivatives as antibacterial agents against E. coli and Staphylococ cus aureus on theoretical basis, we establi-shed a quantitative structure activity relationship between their antibacterial activity and descriptors coding for molecular properties; 2D autocorrelations, 2D matrix-based descriptors, Connectivity indices of molecules under consideration using described by Hansch and Free & Wilson. [19,20,21]

In the present study, a data set of 25 monoterpenes derivatives was subjected MLR analysis for model generation. The reference drugs were not included in model development as they belong to different structural series. Antibacterial activity (E. coli and Staphylococcus aureus) data determined as pMIC Minimum inhibitory concentration compared to the quantitative structure activity relationship model, which provides details linking chemical and inhibitory activities, Table-2 which was used as a dependent variable in the QSAR study. Different structural molecular descriptors were used as independent variable and were correlated with inhibitory activity.

Developing a QSAR model requires a diverse set of a data and there by a large number of descriptors have to be considered descriptors are numerical values that encode different structural features of the molecules selection of a set of appropriate descriptors from a large number of them requires a method, which is able to discriminate between the parameters. Pearson's correlation matrix has been performed on all descriptors by using NCSS statistical Software [22]. The analysis of the matrix revealed six descriptors for the development of MLR model. The value of descriptors selected for MLR model are presented in Table 2 these parameters are calculated using the software dragon supplied by Vcc lab[23].

Table 3(A): Correlation matrix for antibacterial activity of monoterpenes derivatives against S.aureus

	$MIC_{S.aureus}$	GGI7	ATS3s	ATSC1s	SpPosA_B(i)	X4Av	Chi_Dz(e)
MIC	1						
GGI7	0.408436	1					
ATS3s	0.422658	-0.22125	1				
ATSC1s	0.118137	0.089837	0.719685	1			
SpPosA_B(i)	0.276142	0.314991	0.204538	-0.00723	1		
X4Av	-0.41956	-0.78255	-0.09952	-0.40358	-0.41736	1	
Chi_Dz(e)	0.068695	-0.71892	0.470794	-0.06823	-0.04345	0.61342	1

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 114-126 www.ijprajournal.com ISSN: 2456-4494

Table 3(B): Correlation matrix for antibacterial activity of monoterpenes derivatives against E.coli

	MIC	GGI7	ATS3s	ATSC1s	SpPosA_B(i)	X4Av	Chi_Dz(e)
MIC	1						
GGI7	0.472828	1					
ATS3s	0.226429	-0.22125	1				
ATSC1s	-0.08884	0.089837	0.719685	1			
SpPosA_B(i)	0.216821	0.314991	0.204538	-0.00723	1		
X4Av	-0.37473	-0.78255	-0.09952	-0.40358	-0.41736	1	
Chi_Dz(e)	0.027129	-0.71892	0.470794	-0.06823	-0.04345	0.61342	1

The data presented in Table-3 demonstrated the high co linearity between the parameters (r>0.7) except ATS3s and ATSC1s. This high co linearity indicated that these parameters couldn't be combined to get multiple linear regression models. If combined, the low co-linearity between the parameters (r<7) indicated that these parameter could be combined to get MLR models. The analysis of matrix revealed molecular properties; 2D autocorrelations, 2D matrix-based descriptors, Connectivity indices for the development of (MLR) models.

Validations are a crucial aspect of any QSAR analysis. The statistical quality of the resulting model as depicted in Table-4(A&B) are determined by R^2= regression coefficient, MSE= means of standard error of estimations, F-ratio and Q=$\sqrt{R2}$/ MSE; Quality factor.

After performing regression analysis, we have adopted maximum R^2 method, followed by stepwise regression analysis. The result has show that for the set of 25 compound mono-parametric regressions start giving statistically significant model. The best developed model is given below.

The molecular properties; 2D autocorrelations, 2D matrix-based descriptors, Connectivity indices data was subjected to regression analysis Table-4.12.4(A) & (B) and the best mono parameters model is given below.

QSAR model for antibacterial activity against Gram-positive S.aureus

$pMIC_{S.aureus}$=1.2429 +0.2864(± 0.1280) ATS3s

N=25, MSE=0.03532,AR2=0.1429,R2=0.1786,F-ratio=5.002, Q-value=2.24869…Eq-1

Here N is the number of compounds, SE= standard error of the estimation, R^2 is the regression coefficient, AR2 is the adjusted regression coefficient, F-ratio= Fischer statistics and Q-value is the quality factor. From above mono parametric model it is clear that ATS3s that represents the positive correlation of molecular descriptors with antibacterial activity A positive correlation with the ATS3s indicates that the magnitude of the antibacterial activity of monoterpenes derivative against Gram-positive S.aureus is directly proportional to the ATS3s value. The variance coefficient of developed model Eq-1 is founded low which indicates that the model is not statistically significant and the addition of descriptors results the development of bi-parametric model Eq-2.

$pMIC_{S.aureus}$= 0.7877 + 2.3671(± 0.7314) GGI7+0.3655 (±0.1105) ATS3s

N=25, MSE=0.02502,AR2=0.393,R2=0.4436,F-ratio=8.769, Q-value=4.21067…Eq-2

The developed QSAR model Eq-2 describing the importance of Molecular properties; GGI7,ATS3s 2D autocorrelations descriptors in the case the positive correlation was observed between GGI7,ATS3s therefore the antibacterial activity against **Gram-positive** S.aureus will increase with an increase in the value of GGI7,ATS3s variance is not very high about 44%. So future addition another parameters is required regression monoterpenes derivatives.

$pMIC_{S.aureus}$= 0.5919+3.2617(±0.6053) GGI7+0.7668(±0.1312)ATS3s-0.0261 (±0.0065) ATSC1s

N=25, MSE=0.01482,AR2=0.6405,R2=0.6854,F-ratio=15.25, Q-value=6.8006 ….Eq-3

$pMIC_{S.aureus}$= 1.7749+3.9387(±0.6564)GGI7+0.9106 (±0.1415)ATS3s-0.0319 (±0.0067)ATSC1s-2.2847 (±1.1276)SpPosA_B(i)

N=25, MSE=0.012911,AR2=0.6868,R2=0.7390,F-ratio=14.155, Q-value=7.5655 ….Eq-4

Penta-parametric model

$MIC_{S.aureus}$=4.6583+2.8160(±0.8984)GGI7+0.9434(±0.1361)ATS3s-0.0377 (±0.0072)ATSC1s-3.0604 (±1.1631)SpPosA_B(i)-62.6886 (±36.0105)X4Av

N=25, MSE=0.01172,AR2=0.7156,R2=0.7749,F-ratio=13.08, Q-value=8.1312 ..Eq-5

The QSAR model described by Eq-3 to Eq-5, demonstrated the importance of GGI7, ATS3s, ATSC1s and SpPosA_B(i),X4Av indices in describing the antibacterial activity

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 114-126 www.ijprajournal.com ISSN: 2456-4494

against **Gram-positive** S.aureus. the positive correlation is shown by GGI7 and ATS3s with antibacterial activity reveals that increase in value of molecular descriptor GGI7 and ATS3s will lead to increase in antibacterial activity against S.aureus while negative coefficient is shown by ATSC1s and SpPosA_B(i), X4Av with antibacterial activity reveals that decrease in value of molecular descriptors ATSC1s and SpPosA_B(i), X4Av will lead in antibacterial activity. it is important to note that Eq-3 & Eq-5 was derived using the entire data set as there were three serious outliers in the data set and after the removing these outliers the QSAR model no -6 is developed which is statistically significant.

After deletion of outlier compounds no. 3, 19, 22
Finally in order to confirm which out of the proposed model is the most appropriated for modeling the inhibitory.

$pMIC_{S.aureus}$= 5.7221+0.5505 (±0.1219)ATS3s-0.0322 (±0.0054)ATSC1s-177.8603(± 21.8001)X4Av+0.7076(± 0.2899)Chi_Dz(e)

N=22,MSE=0.0049438,AR^2=0.8477,R^2=0.8767,F-ratio=30.225, Q-value=13.318.Eq-6

The Eq.5, derived for the antibacterial activity of synthesized compounds against S.aureus indicated the importance of the 2D autocorrelations ,2D matrix based descriptors with , connectivity indices ATS3s,ATSC1s,Chi_Dz(e) and X4Av in describing the antibacterial activity against S.aureus. The negative correlation of ATSC1s and X4Av with antibacterial activity against Gram-positive S.aureus reveals that a decrease in value of ATSC1s and X4Av will lead to an increase in the antibacterial activity against Gram-positive Staphylococcus aureus. The developed QSAR model is statistically with high regression coefficient between the descriptors and antibacterial activity is **R^2=0.8767**, which is quite good with the variance of **87.6%** with the smallest standard error of estimation. Even though the sample size and the 'rule of thumb' allowed us to go for development of tetra parametric models in MLR analysis, the high parametric model only. The "rule of thumb" gives information about the number of parameters to be selected for regression analysis in QSAR based on the number of compounds. According to this rule for QSAR model development one should select one parameter for a five compounds data set.

QSAR model for antibacterial activity against Gram-negative E.coli

$pMIC_{E.Coli}$ = 2.2366+3.7887(± 1.4722)GGI7

N=25, MSE=0.1066, AR2=0.1898, R2=0.2236, F-ratio=6.623, Q-value=1.4482..Eq-7

Here N is the number of compounds, SE standard error of the estimation, R^2 is the regression coefficient, AR2 is the adjusted regression coefficient, F-ratio= Fischer statistics and Q-value is the quality factor. The coefficient of GGI7 is positive in Eq-7, which indicates that the antibacterial activity will increase with the increase in GGI7 of the synthesized compounds, which can be clearly seen from their antibacterial activity against E.coli.

However to have better model we carried out several multi parametric correlations and those which are statistically are presented in (Table-4.12.4(B).

Di-parametric model

$pMIC_{E.Coli}$ = 0.2672+8.1650 (±1.7336)GGI7+2.4902 (±0.7092)Chi_Dz(e)

N=25, MSE=0.07142, AR2=0.4572, R2=0.5024, F-ratio=11.107, Q-value=2.6522...Eq-8

The developed QSAR model Eq-8 describing the importance of 2D autocorrelations, with 2D matrix-based descriptors in the case the positive correlation was observed between GGI7, and Chi_Dz(e) and antibacterial activity against E.coli will increase with an increase in the value of GGI7,Chi_Dz(e) variance is not very high about 50%. So future addition another parameters is required regression monoterpenes derivatives.

Tri-parametric model

$pMIC_{E.Coli}$ = -2.8288+6.3628(±1.0537)GGI7+1.2992(±0.2283)ATS3s-0.0571 (±0.0113) ATSC1s

N=25, MSE=0.0449, AR2=0.6587, R2=0.7013, F-ratio=16.43, Q-value=3.9521…Eq-9

Tetra-parametric model

$pMIC_{E.Coli}$ = 2.9503+8.0159 (±1.0229)GGI7+1.6504 (±0.2205)ATS3s-0.0711 (±0.0104)ATSC1s 5.5787 (±1.7570)SpPosA_B(i)

N=25, MSE=0.03135, AR2=0.7617, R2=0.8014, F-ratio=20.18, Q-value=5.0559…Eq-10

Penta-parametric model

$pMIC_{E.Coli}$ =7.8044+6.1258(±1.3811)GGI7+1.7055(±0.2093)ATS3s-0.0810(±0.0111)A TSC1s -6.8847(±1.7881)SpPosA_B(I)-105.5345 (± 55.3608)X4Av

N=25, MSE=0.0277, AR2=0.7894, R2=0.8333, F-ratio=18.997, Q-value=5.4848..Eq-11

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 114-126 www.ijprajournal.com ISSN: 2456-4494

For antibacterial activity against E.coli, the developed QSAR model Eq-9-Eq-11 describes the importance of GGI7, ATS3s, ATSC1s, X4Av and SpPosA_B(i). In this case, the positive correlation was observed between GGI7, ATS3s and antibacterial activity against E.coli , while negative correlation is observed between ATSC1s and SpPosA_B(i), X4Av with antibacterial activity. it is important to note that Eq-9 & Eq-11 was derived using the entire data set as there were three serious outliers in the data set and after the removing these outliers the QSAR model no -12 is developed which is statistically significant.

After deletion of outlier compounds no. 1,5,14
Tetra parametric model
$MIC_{E.Coli}$ = 4.6029+8.3238(±0.9062) GGI7+1.7518(±0.2165) ATS3s-0.0813(±0.0102) ATSC1s-7.0361 (±1.6163)SpPosA_B(i)
N=22, MSE=0.02195, AR^2=0.8269, R^2=0.8599, F-ratio=26.086, Q-value=6.259…Eq-12

The Eq.12, derived for the antibacterial activity of synthesized compounds against E.coli indicated the importance of the 2D autocorre lations, with 2D matrix based descriptors, GGI7,ATS3s,ATSC1s and SpPosA_B(i) in describing the antibacterial activity against E.coli. in the QSAR model Eq-12 the 2D autocorrelations, with 2D matrix based descript ors ATSC1s and SpPosA_B(i) have negative coefficient indicates that with the decrease of their values the antibacterial activity increases while GGI7 and ATS3s have positive coefficient indicates that with the increase of their values the antibacterial activity against Gram-negative E.coli also increases. The regression coefficients were found to be good (**0.8599**) in Eq-12 and the means square error of estimation MSE (0.02195). An excellent regression was obtained in Eq-12, where the regression coefficient is maximum with a minimum SE value. Finally, in order to confirm which out of the proposed model is the most appropriated for modeling the antibacterial activity we calculated the pogliani's quality factor Q which is ratio of R and SE standard error of the estimation. This Q value maximum value is found for Gram-positive S.aureus and Gram-negative E.coli (Eq-1 to Eq-12) as (2.24869, 4.21067, 6.8006, 7.5655, 8.1312, 13.318), (1.4483, 2.65225, 3.95211, 5.05599and 6.25903) respectively. The highest value in case of tetra parametric model expressed by Eq-12 suggests that it is the best QSAR model for modeling the antibacterial activity against Gram-negative E.coli.

Table 4.12.4(A) Regression statistical analysis monoterpenes derivative as antibacterial against S.aureus

Model No.	parameter	Ai,i=1,2,3….	Intercept	MSE	AR2	R2	R	F-Ratio	Q-Value
1	ATS3s	A1=0.2864(±0.1280)	1.2429	0.03532	0.1429	0.1786	0.4226	5.002	2.24869
2	GGI7 ATS3s	A1=2.3671(±0.7314) A2=0.3655(±0.1105)	0.7877	0.02502	0.393	0.4436	0.666	8.769	4.21067
4	GGI7	A1=3.2617(±0.6053)	0.5919	0.01482	0.6405	0.6854	0.8279	15.25	6.8006
	ATS3s ATSC1s	A2=0.7668(±0.1312) A3=-0.0261(±0.0065)							
7	GGI7 ATS3s ATSC1s SpPosA_B(i)	A1=3.9387(±0.6564) A2=0.9106(±0.1415) A3=-0.0319(±0.0067) A4=-2.2847(±1.1276)	1.7749	0.012911	0.6868	0.739	0.8597	14.155	7.5655
10	GGI7 ATS3s ATSC1s	A1=2.8160(±0.8984) A2=0.9434(±0.1361) A3=-0.0377	4.6583	0.01172	0.7156	0.7749	0.8803	13.08	8.1312

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 114-126 www.ijprajournal.com ISSN: 2456-4494

	SpPosA_B(i) X4Av	(±0.0072) A4=-3.0604 (±1.1631) A5=-62.6886 (±36.0105)							
	After deletion of outlier compounds no. 3,19,22								
13	ATS3s ATSC1s X4Av Chi_Dz(e)	A1=0.5505 (±0.1219) A2=-0.0322 (±0.0054) A3=-177.8603(± 21.8001) A4=0.7076(± 0.2899)	5.7221	0.004944	0.8477	0.8767	0.9363	30.225	13.318

Table 4.12.4(B) Regression statistical analysis monoterpenes derivative as antibacterial against E.coli

Model No.	parameter	Ai,i=1,2,3….	Intercept	MSE	AR2	R2	R	F-Ratio	Q-Value
1	GGI7	A1=3.7887(± 1.4722)	2.2366	0.1066	0.1898	0.2236	0.4729	6.623	1.4483
2	GGI7, Chi_Dz(e)	A1=8.1650 (±1.7336) A2=2.4902 (±0.7092)	0.2672	0.07142	0.4572	0.5024	0.7088	11.107	2.65225
4	GGI7 ATS3s ATSC1s	A1=6.3628(± 1.0537) A2=1.2992(± 0.2283) A3=-0.0571 (±0.0113)	-2.8288	0.0449	0.6587	0.7013	0.8374	16.438	3.95211
7	GGI7 ATS3s ATSC1s SpPosA_B(i)	A1=8.0159 (±1.0229) A2=1.6504 (±0.2205) A3=-0.0711 (±0.0104) A4=-5.5787 (±1.7570)	2.9503	0.03135	0.7617	0.8014	0.8952	20.18	5.05599
10	GGI7 ATS3s ATSC1s SpPosA_B(i) X4Av	A1=6.1258(± 1.3811) A2=1.7055 (±0.2093) A3=-0.0810(± 0.0111) A4=-6.8847(± 1.7881) A5=-105.5345 (± 55.3608)	7.8044	0.0277	0.7894	0.8333	0.9129	18.997	5.4848
		After deletion compounds No. 1,5,14							
13	GGI7 ATS3s ATSC1s	A1=8.3238 (± 0.9062 A2=1.7518 (± 0.2165 A3=-0.0813(±	4.6029	0.02195	0.8269	0.8599	0.9273	26.086	6.25903

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 114-126 www.ijprajournal.com ISSN: 2456-4494

	SpPosA_B(i)	0.0102 A4=-7.0361 (± 1.6163							

The various cross validation parameters, calculated for the proposed models, are presented on Table-4.12.5(A)&9(B) and are discussed below.

Table-4.12.5(A) Cross validation statistical parameters (S.aureus)

MODEL NO	NO OF DESCRIPTOR	N	PRESS	SSY	PRESS/SSY	R2	Adj R2	R2CV	PSE	SPRESS
1	ATS3s	25	0.8125	0.1767	4.598	0.1786	0.1429	-3.598	0.1802	0.1879
2	GGI7,ATS3s	25	0.5504	0.4388	1.254	0.4436	0.393	-0.254	0.1483	0.1581
4	GGI7,ATS3s,ATS3s	25	0.3112	0.678	0.4589	0.6854	0.6405	0.5411	0.1115	0.1217
7	GGI7,ATS3s,ATSC1s	25	0.2582	0.731	0.3532	0.739	0.6868	0.6468	0.1016	0.1136
	SpPosA_B(i)									
10	GGI7,ATS3s,ATSC1s	25	0.2227	0.7666	0.2905	0.7749	0.7156	0.7095	0.09438	0.10826
	SpPosA_B(i),X4Av									
13	ATS3s,ATSC1s,X4Av	22	0.08404	0.5977	0.1406	0.8767	0.8477	0.8594	0.0579	0.07031
	Chi_Dz(e)									

Table-4.12.5(B) Cross validation statistical parameters (E.coli)

MODEL NO	NO OF DESCRIPTOR	N	PRESS	SSY	PRESS/SSY	R^2	Adj R^2	R^2_{CV}	PSE	SPRESS
1	GGI7	25	2.45184	0.70598	3.4729	0.2236	0.1898	-2.4729	0.31316	0.3264
2	GGI7,Chi_Dz(e)	25	1.5712	1.5865	0.9903	0.5024	0.4572	0.0097	0.2511	0.2672
4	GGI7,ATS3s,ATSC1s	25	0.94309	2.2147	0.4258	0.7013	0.6587	0.5742	0.1942	0.2119
7	GGI7,ATS3s,ATSC1s	25	0.62704	2.5307	0.2477	0.8014	0.7617	0.7523	0.1583	0.177
	SpPosA_B(i)									
10	GGI7,ATS3s,ATSC1s	25	0.5263	2.6314	0.2	0.8333	0.7894	0.8	0.145	0.1664
	SpPosA_B(i),X4Av									
13	GGI7,ATS3s,ATSC1s	22	0.3731	2.2904	0.1628	0.8599	0.8269	0.8372	0.1273	0.1481
	SpPosA_B(i)									

We have undertaken a cross validation methodology for deciding the predictive power of the proposed model. It is necessary for a best model to have good statistics but this is not sufficient for good predictive potential.

QSAR should be evaluated according to its ability to predict the activity of molecules, which were not used in the original QSAR table, which contains the data, the dependent activity and the independent variables. Such an evaluation can be done by cross-validation method, which is based on 'leave-n-out 'concept. In each step 'N' molecules are randomly or on turn excluded from the QSAR table. The QSAR equation is then calculated and used to predict the activity of these n molecules. The methodology yields cross-validated parameters, PRESS (predictive residual sum of squares), SSY (sum of the square of the response value), R^2 (regression coefficient), R^2_{cv} (overall predictive ability), R^2_A (adjustable $-R^2$) S_{PRESS} (uncertainty of predictive), and PSE (predictive square error). These parameters obtained for the model discussed above is calculated as given in Table4.12.5 (A) & (B).

A perusal of Table4.12.5 (A) & (B) shows that in each case PRESS<<SSY and also that PRESS/SSY <0.4. This indicates that the proposed models are better than chance and indicate them to be excellent models. The PRESS/SSY value for the model no. 13(A&B), that is, 0.1406, 0.1628 indicates to the best model. The R^2_{cv} values also support these findings. The cross-validated parameters S_{PRESS} is not useful as it similar to the SE. The other cross-validated parameters viz., PSE

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 114-126 www.ijprajournal.com ISSN: 2456-4494

is, therefore, used to estimate uncertainty of prediction, the lowest value of PSE (0.0579&0.1273) for the model-13(A&B) establishes it to be the model with best statistics and the best predictive power.

The high R^2_{cv} is indicative of its reliability in predicting the antibacterial activity. But, the only way to estimate the true predictive power of a model is to test their ability to predict accurately the antibacterial activities of compounds.

Based on the magnitude of residue a close agreement between the observed and calculated antibacterial activity against the Gram-positive S.aureus and Gram-negative E.coli is found. Future, the plot of Predicted $MIC_{S.aureus}$ &$MIC_{E.coli}$ values against Observed $MIC_{S.aureus}$ &$MIC_{E.coli}$ values also proves the superiority of the model expressed by Eq. No.6&12 the results of monoterpene derivatives as antibacterial agents against E. coli and Staphylococcus aureus. Are summarized in given below Table.4.12.6.

Table 6 Comparison of observed and predicted antibacterial activity of monoterpenes derivatives

	Eq-11			Eq-12			Eq-5			Eq-6		
	$pMIC_{E.coli}$			$pMIC_{E.coli}$			$pMIC_{S.aureus}$			$pMIC_{S.aureus}$		
Comp.	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.
1	2.732	2.94	-0.208	-	-	-	2.785	2.916	-0.131	2.785	2.906	-0.121
2	2.146	2.112	0.034	2.146	2.193	-0.047	2.439	2.444	-0.005	2.439	2.557	-0.118
3	2.439	2.374	0.065	2.439	2.456	-0.017	2.477	2.586	-0.108	-	-	-
4	2.602	2.574	0.028	2.602	2.66	-0.058	2.74	2.674	0.066	2.74	2.678	0.062
5	1.813	2.099	-0.286	-	-	-	2.415	2.442	-0.027	2.415	2.455	-0.04
6	2.74	2.544	0.197	2.74	2.636	0.104	2.778	2.681	0.097	2.778	2.724	0.054
7	2.748	2.629	0.119	2.748	2.645	0.104	2.903	2.86	0.043	2.903	2.873	0.03
8	2.301	2.143	0.158	2.301	2.135	0.166	2.623	2.566	0.058	2.623	2.716	-0.093
9	2.439	2.494	-0.055	2.439	2.613	-0.174	2.699	2.778	-0.079	2.699	2.681	0.017
10	1.845	2.041	-0.195	1.845	2.027	-0.182	2.602	2.475	0.127	2.602	2.558	0.044
11	1.778	1.917	-0.138	1.778	1.901	-0.123	2.585	2.42	0.165	2.585	2.587	-0.002
12	2.255	2.066	0.189	2.255	2.169	0.086	2.462	2.427	0.036	2.462	2.46	0.002
13	2.439	2.332	0.107	2.439	2.425	0.014	2.74	2.603	0.137	2.74	2.663	0.078
14	2.13	2.369	-0.239	-	-	-	2.398	2.561	-0.163	2.398	2.438	-0.04
15	2.398	2.238	0.16	2.398	2.345	0.053	2.477	2.503	-0.026	2.477	2.455	0.022
16	2.114	1.975	0.139	2.114	1.966	0.148	2.423	2.463	-0.04	2.423	2.468	-0.045
17	2.439	2.22	0.22	2.439	2.21	0.229	2.602	2.555	0.047	2.602	2.551	0.051
18	1.74	1.905	-0.165	1.74	2.001	-0.261	2.352	2.405	-0.053	2.352	2.341	0.012
19	1.653	1.731	-0.077	1.653	1.711	-0.058	2.13	2.337	-0.207	-	-	-
20	2.724	2.699	0.025	2.724	2.897	-0.173	2.829	2.737	0.092	2.829	2.738	0.091
21	2.591	2.6	-0.009	2.591	2.577	0.015	2.653	2.743	-0.09	2.653	2.728	-0.075
22	2.699	2.746	-0.047	2.699	2.547	0.152	2.813	2.867	-0.054	-	-	-
23	2.602	2.483	0.119	2.602	2.457	0.145	2.778	2.691	0.087	2.778	2.744	0.035
24	2.778	2.862	-0.084	2.778	2.809	-0.031	2.929	2.922	0.007	2.929	2.971	-0.042
25	2.74	2.794	-0.053	2.74	2.833	-0.092	2.898	2.877	0.021	2.898	2.822	0.075

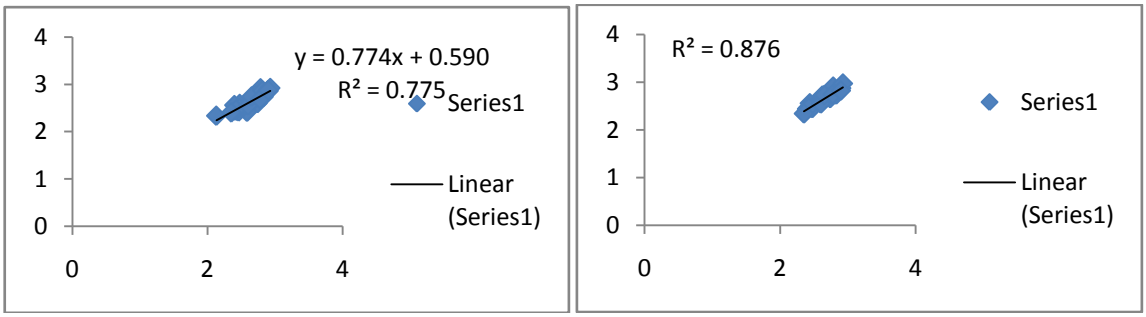


Fig 4.12.1(A)- Graph between predicted and observed p**$MIC_{S.aureus}$ values of monoterpenes derivatives (from Eq-5 & Eq-6)**

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 114-126 www.ijprajournal.com ISSN: 2456-4494

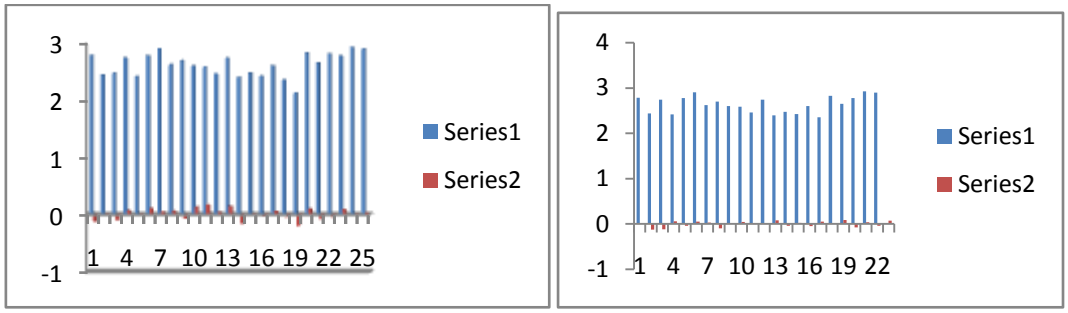


Fig 4.12.2(A)- Plot of the residual values again the experimental observed p**MIC$_{S.aureus}$ values of monoterpenes derivatives (From Eq-5 &Eq-6)**

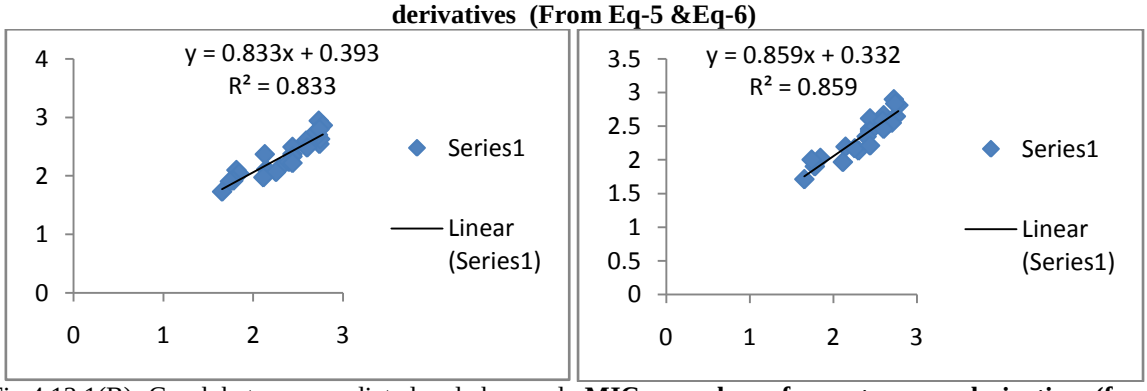


Fig 4.12.1(B)- Graph between predicted and observed p**MIC$_{E.coli}$ values of monoterpenes derivatives (from Eq-11 & Eq-12)**

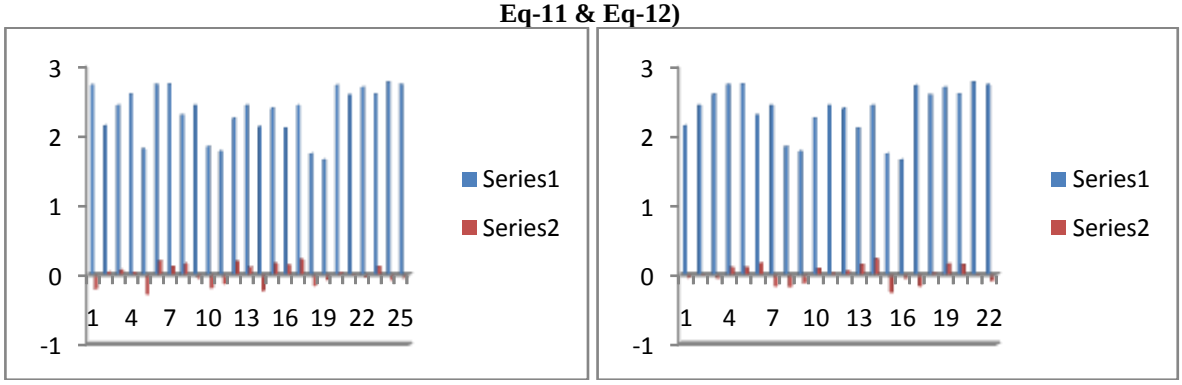


Fig 4.12.2(B)- Plot of the residual values again the experimental observed p**MIC$_{E.coli}$ values of monoterpenes derivatives (From Eq-11 &Eq-12)**

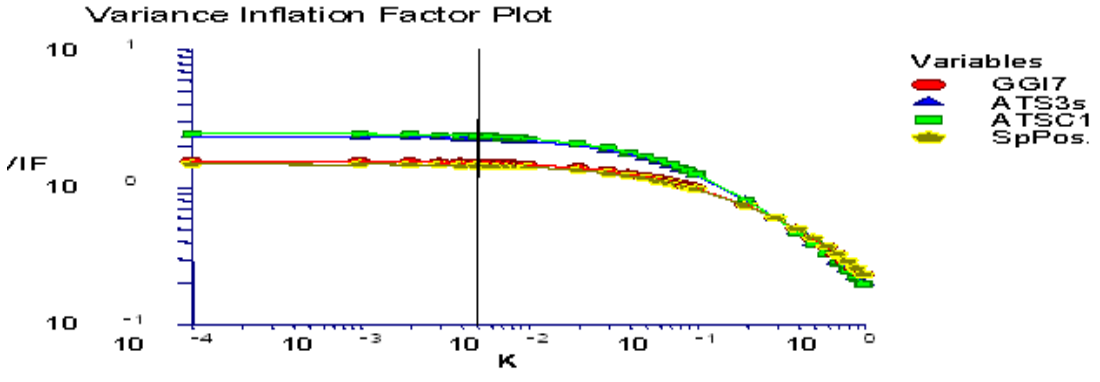


Fig 4.12.3- Variance inflation factor plot

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 114-126 www.ijprajournal.com ISSN: 2456-4494

V.CONCLUSION

According to the results and discussions shown above, the monoterpene derivatives were more effective versus Gram positive S. aureus and Gram negative E. coli. A series of monoterpene derivatives'
antimicrobial activities against E. coli and Staphylo coccus aureus is predicted using QSAR models bas ed on the QSAR findings of the study. Multiple line ar regression for the total data set of 25 compounds in the present study with antibacterial activity demo nstrated that the 2D autocorrelations, with 2D matri x based descriptors,(GGI7)Topological charge index of order 7, (ATS3s) Broto-Moreau autocorrelation of lag 3 (log function) weighted by I-state (ATSC1s) Centred Broto-Moreau autocorrelation of lag 1 weighted by I-state and (SpPosA_B(i)) normalized spectral positive sum from Burden matrix weighted by ionization potential appears to be the governing factor for the antibacterial potency of synthesized monoterpenes derivatives. The antibacterial activity of the synthesised monoterpene derivatives against Gram-positive S. aureus and Gram-negative E. coli was predicted using a mathematical model. There was good agreement between the predicted and experimental values. Low residual activity and a high cross-validated R^2 value (R^2_{CV}) were found, which demonstrated the created QSAR model's ability for prediction. The results suggest that this model may be used to accurately predict the antibacterial activity of various groups o f monoterpene compounds.

VI.ACKNOWLEDGEMENTS

We are grateful to **Dr. V.K. Agrawal**, retired Professor of chemistry at A.P.S. University, Rewa, for his valuable advice and inspiration in carrying out this research. One of the authors, **Dr. Shailja** Sachan**,** associate Professor, Dept. of Chemistry, M. S. Golvalkar College,Rewa is particularly thankful to UGC Bhopal for financial support to purchase NCSS and E-dragon software used in this work, without which this would not have been possible.

REFERENCES

[1]. Gyawali, R., Ibrahim, S.A., 2014. Food Control 46, 412–429.
[2]. Smid, E.J., Gorris, L.G.M., 1999. Natural antimicrobials for food preservation. In: Rahman, M.S. (Ed.), Handbook of Food Preservation. CRC Press, pp. 285–308
[3]. Tajkarimi, M.M., Ibrahim, S.A., Cliver, D.O., 2010. Food Control 21, 1199–1218.
[4]. Gyawali, R., Ibrahim, S.A., 2012. Appl. Microbiol. Biotechnol. 95, 29–45.
[5]. Myszka, K., Leja, K., Majcher, M., 2019. J. Essent. Oil Res. 31, 1–18.
[6]. Rafiq, R., Hayek, S.A., Anyanwu, U., Hardy, B.I., Giddings, V.L., Ibrahim, S.A., Tahergorabi, R., Kang, H.W., 2016. l. Foods 5, 28.
[7]. Stojković, D., Petrović, J., Soković, M., Glamočlija, J., Kukić-Marković, J., Petrović, S., 2013. J. Sci. Food Agric. 93, 3205–3208
[8]. Dorman, H.J.D., Deans, S.G., 2000. J. Appl. Microbiol. 88, 308–316.
[9]. Raho, G.B., Abouni, B., 2015. Escherichia coli and staphylococcus aureus most common source of infection. In: Méndez-Vilas, A. (Ed.), The Battle against Microbial Pathogens: Basic Science, Technological Advances and Educational Programs.
[10]. Karch, H., Tarr, P.I., Bielaszewska, M., 2005. Int. J. Med. Microbiol. 295, 405–418.
[11]. Mayton, H.M., Marcus, I.M., Walker, S.L., 2019. Food Microbiol. 78, 134–142
[12]. Cody, S.H., Glynn, M.K., Farrar, J.A., Cairns, K.L., Griffin, P.M., Kobayashi, J., Fyfe, M., Hoffman, R., King, A.S., Lewis, J.H., 1999. Ann. Intern. Med. 130, 202–209.
[13]. Thompson, L.A., Darwish, W.S., 2019. J. Toxicol. 2019 (14 pages).
[14]. Sharma, V.K., Dean-Nystrom, E.A., 2003. Vet. Microbiol. 93, 247–260
[15]. Jitendra V. Vijay M.K.Evans C.C. Curr.Top.Med.Chem.2010; 10: 95-115.
[16]. Tropsha A. et.al. Mol.Inf.2010; 29: 476-488.
[17]. Talele T.T, Santosh A.K., Alan C.R. Curr. Top. Med. Chem.2010; 10: 127-141.
[18]. Badawy. M.E.I, Kh. Gwhan I. Pesticide Biochemistry and Physiology.2019; 158: 185-200.
[19]. Hansch C, Fujita (1964) . J Am. Chem.Soc. 86: 1616-1626.
[20]. Kubinyi H (1976). Quant. Struct. Act. Relat. 7, 121,-133
[21]. S M FREE Jr and Wilson J W. J. Med Chem. 1964; 7: 395-399
[22]. NCSS, statistical analysis softwhere. www.ncss.com (Accessed May 2005)

[23]. 23 Talete Srl, DRAGON V.6.0 p.(2010) software for Molecular Descriptors Calculation.