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Quantitative Structure−Activity Relationship of Terpenoid Aphid Antifeedants

ZONGDE WANG,[†] JIE SONG,*[,‡] ZHAOJIU HAN,[§] ZHIKUAN JIANG,[§] WEIQING ZHENG,[†] JINZHU CHEN,[†] ZHANQIAN SONG,[||] AND SHIBIN SHANG[||]

College of Forestry, Jiangxi Agricultural University, Nanchang 330045, China, Department of Chemistry and Biochemistry, University of Michigan—Flint, Michigan 48502, Military Medical Institute of Nanjing Command, Nanjing 210002, China, and Institute of Chemical Industry of Forest Products, Chinese Academy of Forestry, Nanjing 210042, China

A series of terpenoid compounds containing a six-member-ring were synthesized from α- and β-pinenes. Antifeedant activity of these terpenoid compounds were tested on the aphid, *Lipaphis erysimi* (Kalt.), with promising results. Stepwise regression was applied to study the quantitative structure−activity relationship of these compounds. The statistically best model showed that the relative number of O atoms, molecular volume, HOMO−LUMO energy gap, and total charge on the positively charged fragments were the most statistically significant descriptors to predict the antifeedant activity. The possible mechanism of interaction between the antifeedant and aphid chemoreceptor was discussed.

KEYWORDS: Antifeedant activity; terpenoid compound; *Lipaphis erysimi*; QSAR; best multilinear regression; stepwise regression; heuristic regression

INTRODUCTION

Pest control in agriculture and related fields often relies on the use of toxic broad-spectrum insecticides. Because insecticides act on the central nervous system of insects and then produce population suppression, continuous applications of insecticides may lead to the unintended adverse impacts on natural enemies and other nontarget organisms (including human beings) and even the development of resistance (*1*). Unlike insecticides, insect antifeedants, a class of secondary metabolites from natural sources (*2*), modify behavior through targeting the peripheral sensilla instead of the central nervous system (*3*). Advantages of antifeedants over insecticides include easier degradation, rare development of resistance by insects, and less harm to humans, animal, and plants (*4*).

Currently, most developed and applied antifeedants are terpenoids. Among these terpenoids, ajugarin (*5*), azadirachtin (*6*), and polygodial (*7*) have been applied to fields in several countries with promising results having been observed (*8*−*10*). Terpenoid antifeedants usually have complex structures and are primarily extracted from plant sources (e.g., neem seed or polygonum) (*1*). There are restrictions to the large scale production of terpenoid antifeedants. As secondary metabolites with low concentrations in plants, extraction of terpenoid antifeedants from plants is difficult and has a low yield. Chemical synthesis of terpenoid antifeedants, an alternative to extraction, is problematic given the complicated molecular structure and chiral centers of antifeedants that make their synthesis time-consuming and expensive (*11, 12*). As a feasible solution, natural terpenoid materials can be chemically modified with similar structures and chiral centers.

Recently, a group of terpenoid antifeedants was synthesized from turpentine oils, whose main components are α-pinene and β-pinene (*13*). Several of these antifeedants showed promising biological activity in *Lipaphis erysimi* (Kalt.). Synthesis of more effective antifeedants requires deeper understanding of the structure−activity relationship of terpenoid antifeedants. Previous studies have shown that some molecular descriptors, substitution (*14*−*17*), boiling point (*18*), lipophilicity (*19*), conformation, charge distribution (*20*), geometry (*21*), HOMO energy, and LUMO energy (*22*), may predict the capability of antifeedants. However, a systematic study of the quantitative structure−activity relationship (QSAR) of terpenoid antifeedants is unavailable.

In this study, a series of terpenoid compounds, synthesized from α- and β-pinenes, are used to study the statistical relationship between chemical structure and antifeedant activity in *L. erysimi*. QSAR models are built using Codessa (*23*). Based on the QSAR model, the possible mechanism of interactions between antifeedant and *L. erysimi* receptors are discussed.

MATERIALS AND METHODS

Insect. Apterous adult *L. erysimi* were collected from the garden at the Agricultural Academy-Jiangsu Province and reared in an entomo-

* To whom correspondence should be addressed. Phone: +1 810 762 3275. Fax: +1 810 766 6693. E-mail: jiesong@umich.edu.
[†] Jiangxi Agricultural University.
[‡] University of Michigan—Flint.
[§] Military Medical Institute of Nanjing Command.
[||] Chinese Academy of Forestry.

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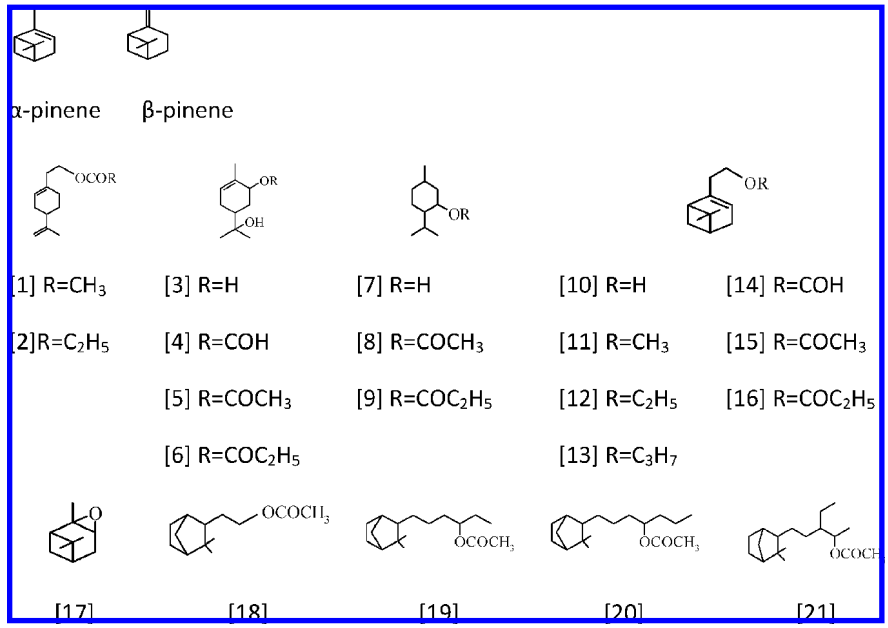

Figure 1. Structures of the test compounds.

logical laboratory on the leaves of cabbage. The temperature and relative humidity in the laboratory were respectively maintained at 25 ± 2 °C and 65 ± 5%.

Test Compounds. Twenty-one compounds were synthesized from α- and *β*-pinene (**Figure 1**). All compounds have a six-member ring with at least one O-containing substituent. Compounds were synthesized in the following ways: (1) four-carbon ring opening reaction involving α- or *β*-pinene (*24, 25*), compounds **1**−**9**; (2) Prins reaction involving *β*-pinene (*26, 27*), compounds **10**−**17** with the structure of 6,6-dimethylbicyclo[3.1.1] hept-2-ene; (3) isomerization of α-pinene (14), compounds **18**−**21** with the structure of 2,2-dimethylbicyclo[2.2.1.] heptane. Synthesis details and related structure identifications can be found in the provided references.

Antifeedant Bioassay. All samples were diluted to 100 mg/mL using anhydrous ethanol and then to 5 mg/mL using water containing 5% (weight) tween 20. The leaf disks (15 mm in diameter) were cut from cabbage leaves with a cork borer. Only leaves with average thickness and few veins were selected for use. The selected leaf disks were dipped into either the diluted sample solutions or the control solvent and then air-dried. The air-dried disks were placed on a wet filter paper in Petri dishes (90 mm diameter) having small holes with tightly fitted lids. Four treated and four control leaf disks were placed into a cross form alternatively. Thirty apterous adult *Lipaphid erysimi* were selected and transferred to the middle of the Petri dishes. The Petri dishes were placed in the laboratory and the number of the *Lipaphid erysimi* staying on the treated and control leaf disks were examined after every 24 h. The final counts for calculation of the antifeedant ratio (AR) were recorded at 48 h.

AR was calculated using eq 1, where CN is the final number of *L. erysimi* on the control leaf disks and TN is the final number of *L. erysimi* on the treated leaf disks. Because no *L. erysimi* were killed, no correction is required. The results of these experiments are listed in **Table 1**.

$$\mathrm{AR} = \frac{\mathrm{CN} - \mathrm{TN}}{\mathrm{CN} + \mathrm{TN}} \quad (1)$$

Computational Details. In general, there are six categories of descriptors, constitutional, topological, geometrical, electrostatic, quantum chemical, and thermodynamic, that are widely applied in QSAR studies. In this study, the relative number of oxygen atoms (OR) (the fraction of the number of O atoms in the test compound), HOMO energy, LUMO energy, HOMO−LUMO energy gap, molecular volume (MV), molecular surface (MS), dipole moment (DM), and boiling point (BP) were used as descriptors. All compounds in this study have two substituents, one partially negatively charged substituent containing ester, ether, or hydroxyl groups and one partially positively charged substituent containing an alkane group. To investigate the effect of the electron distribution on antifeedant capability, Mulliken charges on both substituents were calculated separately. ChargeI and ChargeII were used as separate descriptors to respectively describe the polarity on each substituent group. In addition, the difference between the total charges on these two substituents, ChargeII − ChargeI, was also used as a descriptor. Among these descriptors, OR is the constitutional descriptor, HOMO, LUMO, and HOMO−LUMO are quantum chemical, MV and MS are geometrical, DM, ChargeI, Change II, and ChargeII − ChargeI are electrostatic descriptors. The values of all descriptors are found in **Table 1**.

Conformational searches were carried out over all structures, and the most stable conformers were optimized at the HF/6−31G(d) level using Gaussian 03 (version D.01) (*28*). Using optimized geometries, surface area and molecular volumes were calculated using Ampac-8 while all other descriptors were calculated using Guassian. Boiling points, calculated by Advanced Chemistry Development (ACD/Laboratories) Software, were taken from SciFinder Scholar (*29*). All regression analyses in this study were performed using Codessa 2.7.10 (*23*).

RESULTS AND DISCUSSION

Several regression methods, best multilinear regression, stepwise regression, and heuristic regression, were applied with the results listed in **Table 2** All three regression methods gave similar descriptors and showed significant increase in R^2 when the number of the descriptors was less than or equal to 4. However, there is negligible change in R^2 when the number of descriptors increases from 4 to 5. In addition, $\overline{R^2}$ was used to include the impact of the number of the descriptors and can be calculated by using equation 2 where n is the number of sample compounds and k is the number of descriptors.

$$\overline{R^2} = 1 - (1 - R^2)\frac{n-1}{n-k-1} \quad (2)$$

As seen in **Table 2**, $\overline{R^2}$ is in good agreement with R^2, which shows the slow increase after the number of descriptors reaches 4. Both stepwise regression and heuristic regression attain a maximum value of $\overline{R^2}$ when the number of the descriptors is four. Furthermore, taking into account the number of samples, F test requirements, and t-test requirements, the number of

Table 1. Antifeedant Ratio and Descriptors of the Terpenoid Antifeedants

ID	AR[a]	log BP[b]	OR[c]	MV [d]	MS[e]	HOMO[f]	LUMO[g]	HOMO−LUMO[h]	log DM[i]	ChargeI[j]	ChargeII[k]	ChargeII − ChargeI[l]
1	0.674	2.4522	0.0571	215.3504	243.6231	−0.3403	0.1824	−0.5227	0.39	−0.3891	0.0070	0.3962
2	0.701	2.4780	0.0526	232.8570	262.0223	−0.3400	0.1827	−0.5227	0.37	−0.3882	0.0069	0.3951
3	0.463	2.4322	0.0667	176.8439	193.4716	−0.3332	0.1839	−0.5171	0.39	−0.3193	0.0339	0.3532
4	0.420	2.4331	0.0938	195.9893	210.8686	−0.3512	0.1727	−0.5238	0.64	−0.3977	0.0518	0.4495
5	0.476	2.4451	0.0857	212.2843	226.8260	−0.3477	0.1753	−0.5230	0.68	−0.4036	0.0483	0.4519
6	0.526	2.4715	0.0789	229.3430	241.3835	−0.3469	0.1769	−0.5238	0.67	−0.4022	0.0473	0.4496
7	0.584	2.3332	0.0323	174.6730	189.4722	−0.4056	0.2194	−0.6250	0.24	−0.3248	0.0224	0.3472
8	0.533	2.3600	0.0556	210.6413	214.0281	−0.4143	0.1969	−0.6111	0.69	−0.4097	0.0423	0.4520
9	0.505	2.3913	0.0513	226.7483	231.1052	−0.4133	0.1983	−0.6116	0.67	−0.4084	0.0412	0.4495
10	0.470	2.3711	0.0333	176.7800	177.6300	−0.3246	0.1814	−0.5060	0.22	−0.3060	0.0197	0.3257
11	0.548	2.3483	0.0303	194.1900	198.2300	−0.3246	0.1816	−0.5062	0.11	−0.3180	0.0205	0.3385
12	0.522	2.3851	0.0278	210.4200	216.9100	−0.3242	0.1819	−0.5061	0.08	−0.3193	0.0206	0.3399
13	0.504	2.4178	0.0256	227.0000	235.1900	−0.3241	0.1820	−0.5061	0.04	−0.3191	0.0206	0.3397
14	0.518	2.4103	0.0625	195.7500	204.0700	−0.3384	0.1670	−0.5054	0.70	−0.3794	0.0239	0.4033
15	0.572	2.4294	0.0571	212.1100	217.5500	−0.3361	0.1692	−0.5053	0.71	−0.3789	0.0219	0.4008
16	0.630	2.4574	0.0526	228.9400	231.9900	−0.3355	0.1698	−0.5053	0.69	−0.3770	0.0219	0.3989
17	0.415	2.2755	0.0370	158.3200	158.5600	−0.3854	0.2156	−0.6009	0.33	−0.5775	0.0387	0.6161
18	0.628	2.3969	0.0541	216.9738	221.8668	−0.4108	0.2005	−0.6113	0.35	−0.3932	0.0236	0.4168
19	0.830	2.4807	0.0408	283.8771	286.0275	−0.4042	0.2007	−0.6049	0.30	−0.4026	0.0115	0.4141
20	0.813	2.5015	0.0385	300.7757	304.8715	−0.4039	0.2007	−0.6046	0.29	−0.4035	0.0115	0.4149
21	0.786	2.4894	0.0385	300.4280	297.1098	−0.4054	0.1997	−0.6051	0.32	−0.4064	0.0111	0.4175

[a] Antifeedant ratio at 48 h after treatment. [b] Boiling point. [c] The relative number of oxygen atoms in each compound. [d] Molecular volume, its unit is Å^3. [e] Molecular surface, its unit is Å^2. [f] Energy of the highest occupied molecular orbit in atomic units. [g] Energy of the lowest unoccupied molecular orbit in atomic units. [h] Energy gap between the highest occupied molecular orbit and the lowest unoccupied orbit in atomic units. [i] Dipole moment. [j] Total charge of the substituent which contains either ester/ether bonds or an ethanol hydroxyl group on the backbone. [k] Total charge of the substituent which contains alkane group. [l] Charge gap between chargeII and chargeI.

Table 2. Comparisons of Different Regression Methods[a]

*n**	best multilinear regression	stepwise regression	heuristic regression
2	$R^2 = 0.7474$	$R^2 = 0.8820$	$R^2 = 0.8820$
	$\overline{R^2} = 0.7193$	$\overline{R^2} = 0.8689$	$\overline{R^2} = 0.8689$
	$F = 26.62$	$F = 67.28$	$F = 67.28$
	$s^2 = 0.0042$	$s^2 = 0.0020$	$s^2 = 0.0020$
	descriptors: MV; OR	descriptors: ChargeII; MV	descriptors: ChargeII; MV
3	$R^2 = 0.9052$	$R^2 = 0.9190$	$R^2 = 0.9348$
	$\overline{R^2} = 0.8885$	$\overline{R^2} = 0.9047$	$\overline{R^2} = 0.9233$
	$F = 54.09$	$F = 64.31$	$F = 81.20$
	$s^2 = 0.0017$	$s^2 = 0.0014$	$s^2 = 0.0012$
	descriptors: ChargeII; LUMO; MV	descriptors: ChargeII; HOMO−LUMO; MV	descriptors: ChargeII; HOMO−LUMO; MS
4	$R^2 = 0.9541$	$R^2 = 0.9571$	$R^2 = 0.9571$
	$\overline{R^2} = 0.9426$	$\overline{R^2} = 0.9464$	$\overline{R^2} = 0.9464$
	$F = 83.22$	$F = 89.31$	$F = 89.31$
	$s^2 = 0.0009$	$s^2 = 0.0008$	$s^2 = 0.0008$
	descriptors: ChargeII; LUMO; MV; OR	descriptors: ChargeII; HOMO−LUMO; MV; OR	descriptors: ChargeII; HOMO−LUMO;MV; OR
5	$R^2 = 0.9605$	$R^2 = 0.9575$	$R^2 = 0.9578$
	$\overline{R^2} = 0.9473$	$\overline{R^2} = 0.9433$	$\overline{R^2}1 = 0.9437$
	$F = 72.86$	$F = 67.60$	$F = 68.06$
	$s^2 = 0.0008$	$s^2 = 0.0009$	$s^2 = 0.0008$
	descriptors: ChargeII; LogDM; LUMO; MV; OR	descriptors: ChargeII; HOMO−LUMO; LogDM; MV; OR	descriptors: ChargeII; HOMO; LogDM; LUMO; MV; OR

[a] Definitions of descriptors are given in Table 1.

descriptors used in the final model should not be more than four in order to achieve 95% confidence (*30*). On the basis of these observations, only the stepwise regression method was used for further study.

Stepwise regression involves reduction in the number of molecular descriptors, followed by a *t*-test for the significance of individual descriptors within the model (*31*). Descriptors with high *t* values were accepted and those with low *t* values were rejected. A "breaking point" indicates that the improvement of the regression model has become insignificant ($\Delta R^2 < 0.02 - 0.04$). Seen in **Figure 2**, the breaking point occurs at four descriptors with the values of these descriptors listed in **Table 2**.

The statistically best QSAR model for AR data has the following statistical characteristics: $R^2 = 0.9571$, $F = 89.31$, $s^2 = 0.0008$. The four descriptors in the QSAR model are listed in **Table 3** in order of descending statistical significance, where

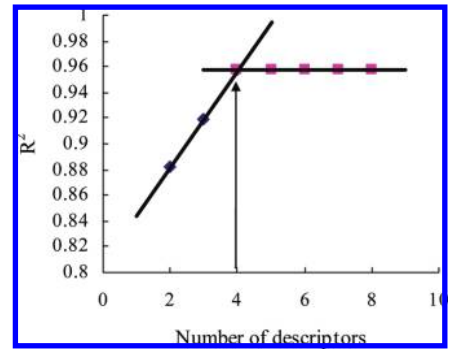

Figure 2. Breaking point rule results.

X and ΔX are the regression coefficients and their standard errors. A graphical representation of the comparison between experimental and predicted AR using the model described in **Table 3** is provided in **Figure 3**.

Table 3. Best Four-Descriptor QSAR Model ($R^2 = 0.9571$, $F = 89.31$, $s^2 = 0.0008$)

descriptor	X	ΔX	t test	descriptor[a]
0	-1.0293×10^{-1}	8.2102×10^{-2}	−1.2537	Intercept
1	−6.3257	7.2676×10^{-1}	−8.7040	ChargeII
2	1.5251×10^{-3}	2.1106×10^{-4}	7.2257	MV
3	-7.5965×10^{-1}	1.5369×10^{-1}	−4.9427	HOMO−LUMO
4	1.8454e	4.8931×10^{-1}	3.7716	OR

[a] Definitions of descriptors are given in Table 1.

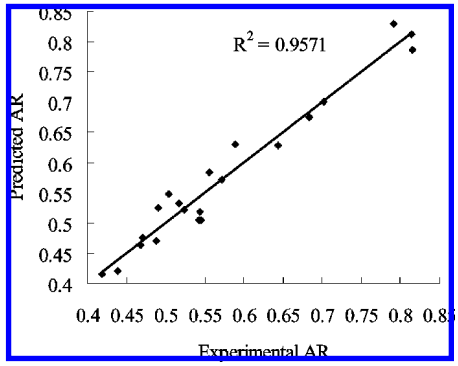

Figure 3. Experimental AR versus predicted AR.

Table 4. Internal Validation of the QSAR Model[a]

training set	N	R^2_{fit}	F	s^2	test set	N	R^2_{pred}	F	s^2
A+B	14	0.9495	42.33	0.0011	C	7	0.9707	165.59	0.0004
A+C	14	0.9495	42.33	0.0011	B	7	0.9690	156.31	0.0007
B+C	14	0.9747	86.69	0.0005	A	7	0.9288	65.26	0.0017
average		0.9579	57.12	0.0009			0.9562	129.05	0.0009

[a] The ID number of A, B, C: A: 1, 4, 7, 10, 13, 16, 19; B: 2, 5, 8, 11, 14, 17, 20; C: 3, 6, 9, 12, 15, 18, 21.

The obtained QSAR model was validated using both internal validation and the "leave-one-out" approach. Internal validation was carried out by dividing the parent data points into three subsets (A−C): the first, fourth, seventh, etc., data points going into the first subset (A), the second, fifth, eight, etc., going into the second subset (B), and the third, sixth, ninth, etc., going into the third subset (C). Two of three subsets, (A and B), (A and C), and (B and C), makeup the training set while the remaining subset is treated as a test set. The correlation equations were derived for each of the training sets using the same descriptors and then applied to predict values for the corresponding test set. Internal validation results are given in **Table 4**. The R^2_{pred} and R^2_{fit} are within 5% for all three sets, and the average values of R^2_{pred} and R^2_{fit} are close to the overall R^2. Therefore, the QSAR model obtained demonstrates the predictive power when 3-fold cross-validation is performed. The "leave-one-out" approach was completed in a similar manner to the internal validation. In the "leave-one-out" approach, every fourth compound is taken and put into an external test set and the remaining compounds are left in the training set. The QSAR model containing the same four descriptors was obtained with $R^2 = 0.9513$ from the training set. When the same QSAR model was applied on the external set, $R^2_{pred} = 0.9745$ was observed. These validation results indicate that the QSAR model obtained is statistically significant.

Although substantial progress has been made in investigating the organization of insect odor and taste receptors, understanding of how these receptors function is still limited. The QSAR model developed in this study reveals how chemical structures of terpenoid antifeedants affect biological activity. This supplies chemical insight into the functional analysis of insect odor and taste receptors.

It has been reported that molecular size is an important factor how to reach active sites or interact with the amine group on insect chemoreceptor, and further, to affect biological activities (*32*). As explained by the lock−key model and induced-fit model hypothesis, molecular recognition of chemical compounds by receptors determines the biological activity (*33, 34*). In this study, molecular volume is one of the statistically significant descriptors in the final model obtained in this study, similar to the conclusion of Sodano et al. (*32*).

Previous research indicates that an efficacious antifeedant should react/interact with primary amine or sulfydryl groups on the insect's chemoreceptor (*35, 36*). Though the interaction/reaction mechanism with these groups is still unclear, the presence of O atom-containing functional groups in antifeedants is considered important (*37, 38*). The presence of O atom-containing functional groups likely alters the electron distribution in the molecule and the electrostatic interactions between the antifeedant and receptor. For example, the addition of hydroxyl or ketone groups to antifeedant structures is known to increase antifeedants activity (*29*).

Results show that both OR and ChargeII are statistically significant descriptors. This implies that the positively charged substituent may be involved in interaction of antifeedants with the chemoreceptor of *L. erysimi*. This finding is in agreement with similar studies by Bravo (*39*). However, OR, instead of ChargeI, is considered statistically significant. Unlike ChargeI, the partial charge of the substituent, OR, represents the fraction of O atoms in the whole molecule. The existence of electronegative O atoms will change the electron distribution among the whole molecule and likely enhance the electrophilic character of the antifeedant compounds. This may indicate that interactions take place between electrophilic sites on the antifeedants and nucleophilic sites on the *L. erysimi* chemoreceptor.

HOMO and LUMO energies, respective measures of nucleophilicity and electrophilicity, are two parameters for description of electron donating/accepting power (*40*). In most cases, the HOMO−LUMO energy gap is widely used as a measure of chemical reactivity (*41−44*) with bigger gaps implying larger excitation energies and higher stability. It has been shown that the energetic properties of the molecule may be important to the antifeedant activity profile.

The HOMO−LUMO energy gap was found be a significant descriptor in the final statistic model. As seen in **Table 1**, all compounds have energy gaps greater than 0.5 H, indicating their stability. Although neither HOMO nor LUMO appear in the final result, our analysis also demonstrates the high correlation between HOMO and HOMO−LUMO ($R^2 = 0.97$). This may suggest that the more effective antifeedant should be stable and in favor of electrophilic interactions with the receptor.

On the basis of results obtained in this study, substrate specificity involving strong electrophilic interactions between terpenoid compounds and the chemoreceptor may help explain the mechanism of antifeedant activity. Though this study is preliminary with further interdisciplinary research being needed, the obtained model furthers understanding on the antifeedant mechanism and supplies guidance in the design of new more effective antifeedants.

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