The antimicrobial quantitative relationship and mechanism of plant flavonoids to gram-positive bacteria

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Abstract

Antimicrobial resistance (AMR) poses a serious threat to human health, and new antimicrobial agents are desperate in need. Plant flavonoids have been increasingly paid attention to, for their antibacterial activities, combinational effects on enhancing the antibacterial activity, and reversing the AMR. Based on our previous work, another two regression equations were established once again between the minimum inhibitory concentrations (MICs) (y) and the lipophilicity parameters ACD/LogP or LogD (x). After comparing the fitting goodness of four equations including two published by us, the best one, regarded as the antimicrobial quantitative relationship of plant flavonoids to gram-positive bacteria, was $y = -0.1285x^6 + 0.7944x^5 + 51.785x^4 - 947.64x^3 + 6638.7x^2 - 21273x + 26087$, and here x is the LogP value. From this equation, the MICs of most plant flavonoids to gram-positive bacteria can be calculated. The minimum MIC was also predicted as approximately 0.9644 μM , and likely from 0.24 to 0.96 μM . Further, this more reliable equation further proved that the lipophilicity is a key factor of plant flavonoids against gram-positive bacteria. Combined with the antibacterial mechanism suggested in our previous work and the support from recent literature, more intuitive evidence powerfully confirmed the antibacterial mechanism that the cell membrane is the major site of plant flavonoids acting on gram-positive bacteria, and that involving the damage of phospholipid bilayers.

Introduction

Antimicrobial resistance (AMR) has been becoming a serious threat to the public health, and the COVID-19 pandemic would further accelerate this global problem¹. So, new antimicrobial agents are in desperate need²⁻³. When antibiotics have been used for the treatment on bacterial infection, most of them will also bring about some adverse reactions, and eventually be resistance in clinic⁴. However, some plant metabolites having moderate antimicrobial activities, being nontoxic to human body, can enhance the antibacterial activity of some antibiotics, and even reverse the AMR⁵. Among them, plant flavonoids have been paid close attention to. Some structure-activity relationships of them against bacteria were sporadically summarized⁵⁻⁷. However, a universality conclusion remains unclear.

In our previous work⁸, two regression equations were established for predicting the antibacterial activities of plant flavonoids to gram-positive bacteria, based on the data pairs of the physicochemical parameter ACD/LogP or LogD_{7.40} and the minimum inhibitory concentrations (MICs) of sixty-six flavonoids reported⁹⁻¹⁴. Subsequently, these two equations were further verified using those of another sixty-eight flavonoids reported^{5,15-20}. Combined literature analysis, we concluded that the lipophilicity is a key factor for flavonoids against gram-positive bacteria, and the cell membrane is the major action site⁸.

Here these data were reanalyzed, and two regression equations were reestablished based on the physicochemical parameter ACD/LogP or LogD_{7.40} and the average MICs (or MIC₉₀) to various gram-positive bacteria, of all flavonoids in our previous work⁸. According to statistical procedure and comparison with those two equations previously reported, a regression equation with a larger correlation

coefficient (r) of 0.9703 was eventually proved as the best one for fitting the correlation between the antibacterial activity and the lipophilicity. This equation shows more accurate and more reliable, and can be practically considered as the quantitative relationship of plant flavonoids against gram-positive bacteria. Moreover, the regression curves established from the $\log_{10}$ (MIC) and the LogP (or LogD_{7.40}) provides a more intuitive fact for the direct correlation between the antibacterial activity to gram-positive bacteria and the lipophilicity, and for the antibacterial mechanism of plant flavonoids acting on the cell membrane. These above were diagrammatically presented as **Fig. 1**.

Results

Structure, antibacterial activity, and physicochemical parameter. One hundred and thirty-four flavonoids reported in twelve papers were reorganized by us^{8,9-20}, ninety-two compounds were screened out, according to the procedure in section *Method*, for subsequent regression analyses. These flavonoids involve twelve subclasses, and which mainly include flavones, dihydroflavones, flavonols, dihydroflavonols, isoflavones, dihydroisoflavones, dihydroisoflavane and chalcones. Their chemical structures were shown on Fig. 1 to 6, and 8 in our previous work⁸, and the numbers of these compounds remains unchanged. Their antimicrobial activities (MICs) and physicochemical parameters (ACD/LogP and LogD_{7.40}) were reorganized and listed in Table 1. If possible, the average MIC or MIC₉₀ of a certain flavonoid to different pathogenic bacteria was considered as its MIC. In other cases, the MIC of a certain flavonoid to pathogenic bacteria was processed according to the rules in section *Method*.

Regression equation from the MICs and the physicochemical parameters. The regression analyses for the MICs (y) to gram-positive bacteria and the physicochemical parameters LogP or LogD_{7.40} (x), of these flavonoids were achieved. Two regression curves were shown on Fig. 1, and two regression equations together with their correlation coefficients (r) were calculated and shown on Fig. 1 and in Table 2.

From Fig. 1, the characteristics of these two regression curves were similar to those established from sixty-six flavonoids⁸. However, they presented larger correlation coefficient (r) values (Table 2), and which better indicated that the significant correlation between the physicochemical parameter LogP or LogD_{7.40} and the MICs of plant flavonoids to gram-positive bacteria, especially for that between the LogP and the MICs as which presented a larger correlation coefficient (r) value of 0.9703 (Table 2). Thereby, these two equations have a greater potency to further prove that the antibacterial activities of plant flavonoids to gram-positive bacteria is close related to their lipophilicities.

Antimicrobial quantitative relationship. Including two regression equations reported by us⁸, four regression equations were established for the fitting of the correlation between the antimicrobial activity (MIC) and the physicochemical parameter (LogP or Log D_{7.40}). To compare the fitting goodness of these four equations, two statistical parameters, coefficient of determination (R^2) and residual standard deviation (s), were respectively calculated, and presented in Table 3. Generally, the closer the R^2 is to 1,

the higher the goodness of fit, and the closer the predictive value is, on the whole, to the actual one. The smaller s is, the smaller the mean deviation between the predictive value and the actual one. From Table 3, the largest value of the R^2 (0.9413) and the smallest value of s (68.1127) indicated that equation (1) is more reliable and is the best one for fitting the quantitative relationship between the physicochemical parameter and the antimicrobial activity to gram-positive bacteria, of plant flavonoids. Thereout, the MICs of most plant flavonoids to gram-positive bacteria can be roughly calculated from this equation by substituting their LogP values (calculated by ACD/Labs 6.0) into.

Table 1. Plant flavonoids together with their structure types, physicochemical parameters and antimicrobial activities, used for the regression analyses⁸.

Compounds ^a	Structure types	LogP ^b	LogD _{7.40} ^b	MIC (μM) ^c	Log ₁₀ (MIC) ^c
2		5.09	4.92	11.3	1.0531
3		7.02	6.8	8.85	0.9469
4		5.29	5.09	14.7	1.1673
6		7.02	6.81	23.7	1.3747
7		4.18	4.09	25.9	1.4133
8		4.18	3.98	25.9	1.4133
9		5.74	5.5	22.7	1.3560
10		6.52	6.33	5.9	0.7709
11		6.30	6.08	5.7	0.7559
12		7.05	6.83	5.5	0.7404
13		7.27	7.09	5.7	0.7559
16		7.24	7.06	9.15	0.9614
17		4.56	4.37	10.5	1.0212
20		5.56	5.34	52.8	1.7226
21		6.54	6.32	9.15	0.9614
22		6.61	6.39	11.35	1.0550
23		5.18	4.96	85.05	1.9297
24		6.25	5.97	8.05	0.9058
25		7.02	6.81	13.65	1.1351
26		7.32	7.12	10.6	1.0253
27		6.72	6.51	20.4	1.3096
28		3.27	3.04	233.7	2.3687
29		4.60	4.38	84.4	1.9263
30		4.27	4.05	84.1	1.9248
31		4.67	4.46	186.4	2.2704
32		6.10	5.76	107.3	2.0306
33		5.63	5.29	113.6	2.0554
34		4.52	3.84	140.2	2.1467

35	4.52	3.93	140.2	2.1467
36	6.20	5.53	73	1.8633
37	6.72	6.51	9.5	0.9777
38	7.32	7.12	14.75	1.1688
39	8.75	8.54	24.45	1.3883
40	7.32	7.13	24.6	1.3909
41	5.94	5.75	90.8	1.9581
42	7.97	7.78	19	1.2788
43	6.74	6.5	37.9	1.5786
44	8.84	8.64	12.25	1.0881
45	3.79	3.67	251.75	2.4010
46	3.79	3.53	167.8	2.2248
47	3.92	3.59	42.1	1.6243
48	4.67	4.35	61	1.7853
49	4.11	3.67	84.5	1.9269
52	4.51	4.27	87.8	1.9435
53	2.42	2.11	1734.6	3.2392
54	4.64	4.34	88.3	1.9460
55	6.52	6.33	11.05	1.0434
56	8.76	8.7	9	0.9542
57	4.72	4.51	24.25	1.3847
58	6.52	6.33	14.7	1.1673
59	5.89	5.67	17.75	1.2492
60	5.89	5.68	21.3	1.3284
61	6.60	6.35	22.05	1.3434
62	5.81	5.62	28.4	1.4533
63	5.81	5.62	28.4	1.4533
64	4.56	4.37	35.1	1.5453
66	3.19	2.96	734.6	2.8661

67	4.20	3.77	184.7	2.2665
<i>Continued</i>				

Compounds ^a	Structure types	LogP ^b	LogD _{7.40} ^b	MIC (μM) ^c	Log ₁₀ (MIC) ^c
70		3.1	2.32	670.5	0.7597
72		7.33	6.89	5.75	2.9485
73		2.83	2.16	888.1	1.5653
75		8.63	8.17	36.75	0.7284
76		6.59	6.4	5.35	0.8325
77		6.6	6.42	6.8	1.4518
81		4.95	4.82	28.3	1.1508
82		4.95	4.82	14.15	1.5502
86		5.67	5.07	35.5	2.5715
87		3.15	2.91	372.8	2.1166
88		5.38	5.12	130.8	1.7239
89		4.15	3.48	52.95	1.0434
91		6.32	6.32	11.05	1.4031
92		4.41	4.4	25.3	1.4609
93		4.18	4.18	28.9	1.7649
94		6.64	6.63	58.2	3.2186
97		2.62	1.95	1654.3	2.5505
113		3.23	3.1	355.2	2.6985
114		3.4	3.26	499.5	2.1318
115		5.03	4.48	135.45	2.1649
116		4.63	4.07	146.2	2.2399
118		5.69	5.4	45.41	1.2940
119		7.33	7.16	19.68	1.8510
120		5.24	4.69	70.95	2.2398
121		4.7	4.27	173.7	1.5786
122		7.13	6.89	37.9	2.1149
123		4.56	4.27	130.3	2.1318
124		5.47	5.21	135.45	1.9557

125	5.47	5.21	90.3	2.0964
126	4.83	4.67	124.85	1.2765
127	6.69	6.5	18.9	1.6375
128	5.99	5.98	43.4	2.5224
130	5.61	5.59	65.15	1.6721
133	4.1	4.1	47	0.7597

^a: The chemical structures of flavonoids showed in our previous work⁸.

^b: The Log P and LogD_{7.40} values were calculated using software ACD/Labs 6.0.

^c: MIC, minimum inhibitory concentration, and here a processed MIC of a certain flavonoid to various gram-positive including *Staphylococcus aureus*, *S. epidermidis*, or/and *Bacillus subtilis*, etc. was presented; log₁₀(MIC) means Log₁₀ of MIC.

Table 2. Regression equations for the correlation between the physicochemical parameter (x) and the antimicrobial activity (y) to gram-positive bacteria, of plant flavonoids^a

Equation number	Sample numbers (n)	Parameters ^b (x)	Regression equation (r ²)
(1)	92	LogP	$y = -0.1285x^6 + 0.7944x^5 + 51.785x^4 - 947.64x^3 + 6638.7x^2 - 21273x + 26087$ (0.9703)
(2)	92	LogD _{7.40}	$y = 0.2337x^6 - 9.1209x^5 + 146.54x^4 - 1240.3x^3 + 5837.4x^2 - 14534x + 15094$ (0.9462)
(3)	66 ^d	LogP	$y = -1.6745x^5 + 56.143x^4 - 741.93x^3 + 4831.8x^2 - 15531x + 19805$ (0.9349)
(4)	66 ^d	LogD _{7.40}	$y = -1.1474x^5 + 38.802x^4 - 515.39x^3 + 3361.9x^2 - 10789x + 13706$ (0.9309)

^a: The antimicrobial activity (y) was the mean MIC (or MIC₉₀) of a certain flavonoid to gram-positive bacteria mainly including *Staphylococcus aureus*, *S. epidermidis* and *Bacillus subtilis*.

^b: The physicochemical parameter (x) was calculated using software ACD/Labs 6.0.

^c: r , correlation coefficients; the significant level α was set as 0.01, and the critical value of $r_{0.995}$ (90) and $r_{0.995}$ (64) were equal to 0.27 and 0.32, respectively.

^d: The regression equations were established in our previous work⁸.

Table 3. Fitting goodness of the regression equations^a

Equation number	Coefficient of determination (R^2)	Residual standard deviation (s)	Goodness of fit
(1)	0.9413	68.1127	The best
(2)	0.8949	91.1187	—
(3)	0.8740	89.5452	—
(4)	0.8666	92.1391	—

^a: Equations (3) and (4) were reported in our previous work⁸, and thereout the R^2 and s values were calculated from the sixty-six data pairs.

Regression equation from the $\log_{10}$ (MIC) and the physicochemical parameter. Base on the regression equations previously established and literature analyses, the antibacterial mechanism of plant flavonoids acting on the cell membrane of gram-positive bacteria was suggested by us⁸. To better observe the correlation between the antibacterial activity and the lipophilic parameters, the regression analyses for the common logarithm ($\log_{10}$) of MIC (y) to gram-positive bacteria and the LogP or LogD_{7.40} (x), of these plant flavonoids, was further performed. Their regression curves and regression equations, with the correlation coefficient (r) values of 0.8040 and 0.8212, were respectively shown on Fig. 2.

Both r values are greater than 0.27 which was the critical value when α was set at 0.01 and the sample number was 92. This indicates that there is a very significant correlation between the $\log_{10}$ (MIC) and the LogP or LogD_{7.40}. Along with the increase of the LogP or LogD_{7.40} value in an approximate range from 2.0 to 8.0, the $\log_{10}$ (MIC) value will decrease, namely the antibacterial activities will increase. These, more intuitively, demonstrated that the antibacterial activity of plant flavonoids to gram-positive bacteria is directly related to their lipophilicity.

Discussion And Conclusion

Flavonoids are a class of secondary metabolites widely distributing in various parts of the plant, and so far, approximate 10,000 compounds have been discovered. These plant flavonoids have various bioactivities, such as antioxidation, antibiosis, estrogen-like effect, and prevention and treatment of cardiovascular diseases^{5,7,21}. After some of them were discovered to have a potency enhancing the antibacterial effect of some antibiotics, or reversing the AMR^{5,6}, their antibacterial activities have been increasingly paid close attention to.

Based on our previous report⁸, here the correlation between the ACD/LogP or LogD_{7.40} values and the MICs to gram-positive bacteria, of plant flavonoids were further proved by a larger sample ($n=92$), and both r values (0.9703 and 0.9462) of two regression equations were larger than those previously published. Thereby, these were better and more scientific to prove that there is a direct correlation between the lipophilicity and the antibacterial activity, of plant flavonoids. The statistical evaluation procedure, including the calculation and comparison of R^2 and s (Table 3), concluded that equation (1) as $y = -0.1285x^6 + 0.7944x^5 + 51.785x^4 - 947.64x^3 + 6638.7x^2 - 21273x + 26087$, between the LogP value (x) and the MICs (y), is the most reliable and the best one. More importantly, this equation was established on the data of twelve subclasses of flavonoids including seven main subclasses, while those previously published were generated from the data of three subclasses of flavonoids. Thereby, these above together indicated that equation (1) is more scientific, reliable and universal, and can be considered as the antimicrobial quantitative relationship of plant flavonoids to gram-positive bacteria.

As previously reported by Cushnie⁶, many factors, involving the MIC of determination methods and details, may influence on the experimental MIC value, and the antibacterial activities of a compound to different pathogens are varied⁸. Moreover, the LogP value calculated by soft ACD/Labs 6.0 generally was presented as a range. Therefore, the tested MICs would fluctuate within a reasonable range of the actual values, and so the determined MICs would probably range from 1/2× to 2× the predicted one, more likely from 1/4× to 4× the predicted one, since the MICs were generally tested by double dilution method²². Based on these, the MIC (More accurately, MIC₉₀) for a certain compound of flavonoids to gram-positive bacteria can be roughly predicted through the calculation by substituting its ACD/LogP value into equation (1). Furthermore, the minimum MIC of plant flavonoids to gram-positive bacteria can be predicted as approximately 0.9644 μM, and at the time the LogP value of is equal to about 7.055. Considering that the experimental MICs would fluctuate, the minimum MIC tested of plant flavonoids to gram-positive bacteria would more likely range from 0.24 to 0.96 μM.

The MICs of most plant flavonoids to gram-positive bacteria can be correctly predicted from this equation, and even if those flavonoid subclasses were not included when equation (1) was established. For example, the MIC of α -mangostin, a xanthone from mangosteen, against gram-positive bacteria was predicted as 8.16 μM (3.35 μg/mL), and so the MICs tested were deduced to range from 0.84 to 13.4 μg/mL. This is, by and large, in consistent with the determined MIC value of 1 or 0.5 μg/mL (0.5 μg/mL for MIC₉₀)²³, and also approved by the antibacterial tests repeated by two students at different time to *S. aureus* ATCC 25923 in our Laboratory (0.5, 1 or 2 μg/mL for the MICs). Of course, a few of plant

flavonoids probably present incorrect predictions, such as baicalein, a rare 5,6,7-trihydroxyl flavonoid from *Scutellaria baicalensis*. However, the structural modification of baicalein for increasing the lipophilicity of molecules will increase the antibacterial activity²⁴. This indicated that the correlation between the antibacterial activity and the lipophilicity is also suitable for baicalein.

Considering that equation (1) was established from the data pairs of the LogP values in an approximate range of 2.4 to 8.9, and that there are few data pairs in the range of 8.0 to 8.9 when equation (1) was established, the antimicrobial quantitative relationship of plant flavonoids to gram-positive bacteria is more scientific and reliable when used for the antibacterial prediction of plant flavonoids having the LogP value ranged from 2.4 to 8.5. However, this does not exclude that the antibacterial activity of some flavonoids, having the LogP value outside of this range, can be accurately predicted using this equation. Empirically, the LogP can be extended to the range from 2.0 to 8.5.

Moreover, the regression equation established by the parameter LogP showed better fit for the correlation between the antibacterial activity and the lipophilicity than that by the LogD_{7.40} (Table 3). However, the LogD_{7.40} can be regarded as the LogP at pH 7.40, and is better to reflect the actual state of a compound in the medium of MIC determination²². So, the MICs calculated from equation (2), are also references for the antibacterial prediction of plant flavonoids although this equation established by the parameter LogD_{7.40} is not the best one for the antibacterial prediction. Similar to our previous analyses⁸, the more reliable regression equations for a certain subclass of flavonoids, with a larger correlation coefficient (*r*), can be also established for the more accurate prediction of the MICs according to similar procedure, and for the structural design and optimization to obtain more efficient antibacterial activity. It is worth noting that this equation is not necessarily suitable for the antibacterial prediction of all structural derivatives of plant flavonoids, especially those introducing heteroatoms, such as nitrogen and halogen.

As we suggested⁸, the cell-membrane is the major site of plant flavonoids acting on gram-positive bacteria, and which likely involving the disruption or damage of phospholipid bilayers. This was further supported by recent reports^{23,25,26}. Here, more reliable regression equations (1) and (2) further proved that the lipophilicity is a key factor responsible for the antibacterial activity of plant flavonoids to gram-positive bacteria. Powerfully, these together with the regression analyses for the correlation between the log₁₀(MIC) and the LogP or LogD_{7.40} more intuitively confirmed this antibacterial mechanism of plant flavonoids acting on the cell membrane of gram-positive bacteria.

In conclusion, the MICs (*y*) of most plant flavonoids to gram-positive bacteria can be calculated by substituting their physicochemical parameter ACD/LogP (*x*) into the equation $y = -0.1285x^6 + 0.7944x^5 + 51.785x^4 - 947.64x^3 + 6638.7x^2 - 21273x + 26087$. Combined with the antibacterial mechanism suggested by us and the support from recent literature, more reliable equations further proved that the lipophilicity is a key factor of plant flavonoids against gram-positive bacteria, and more intuitive evidence powerfully confirmed the antibacterial mechanism that the cell membrane is the major site of plant flavonoids acting on gram-positive bacteria, and which likely involves the damage of phospholipid

bilayers. Based on these, the antibacterial activity and mechanism of plant flavonoids against gram-positive bacteria were diagrammatically presented as Fig. 1, and some errors in Fig. 9 of our published paper happened to be corrected. Simultaneously, all these above provide good references for exploring the antibacterial activity and mechanism of plant flavonoids against gram-negative bacteria.

Methods

Data and processing. Based on all the data of plant flavonoids in our previous work⁸, the data processing was performed. As no clear MIC value was presented for many flavonoids used for the verification of two regression equations in that paper, such as the MIC of compound **84** expressed as more than one hundred ($>100 \mu\text{M}$), these data were processed according to the rules as follows: 1) Discard all ambiguous data which the MICs expressed as more than a certain value; 2) For the MICs expressed as more than or equal to a certain value, the boundary value is considered as the MIC, such as the MIC for compound **69** as $636.4 \mu\text{M}$; 3) For the MICs expressed as more than a range, the latter is considered as the MIC because it is a clear MIC value, such as the MIC for compound **73** as $888.1 \mu\text{M}$; 4) For the MIC expressed as a range, the mean of two boundary values is considered as the MIC because these two boundary values are the MICs of a certain flavonoid to different pathogenic strains, such as the MIC for compound **71** as $520.3 \mu\text{M}$. Finally, based on the variation tendency of MIC along with lipophilicity parameter LogP or LogD, reported by us, and in view of probable fluctuation at the determination of MICs, the probably outliers were discarded using scatter diagram. All the rest data were used as the data of this article for the subsequent analyses. The physicochemical parameter LogP or LogD_{7.40} (Log_{10} of oil/water distribution coefficient at pH 7.40) was calculated using software ACD/Labs 6.0.

Regression analyses. For establishing the antimicrobial quantitative relationship of plant flavonoids to gram-positive bacteria, the regression analyses between the MICs (y) and the physicochemical parameter LogP or LogD_{7.40} (x) were performed using Microsoft Excel software, and the r value was also calculated. To discover more powerful evidence for supporting the antibacterial mechanism of plant flavonoids acting on the cell membrane of gram-positive bacteria, the MIC was further transformed to the $\log_{10}(\text{MIC})$, and subsequently the regression analyses between the $\log_{10}(\text{MIC})$ (y) and the physicochemical parameter LogP or LogD_{7.40} (x) were further achieved.

Statistical analysis. To ensure which one is more reliable, further statistical analyses were performed for all the regression equations including those reported in our previous paper⁸. In the process, two statistical parameters, coefficient of determination (R^2) and residual standard deviation (s), were respectively calculated according to equations (5) and (6).

$$R^2 = 1 - \frac{\sum(y_i - \hat{y}_i)^2}{\sum(y_i - \bar{y})^2} \quad \text{equation (5)}$$

$$s = \sqrt{\frac{\sum(y_i - \hat{y}_i)^2}{n-2}} \quad \text{equation (6)}$$

Where $\hat{y}_i$ is the MIC of a certain flavonoid i ; Correspondingly, $\hat{y}_i$ is the prediction MIC of flavonoid i , $\bar{y}$ is the mean MIC of all flavonoids in Table 1, and n ($n = 92$) is the number of all flavonoids.

When comparing the goodness of fit of these regression curves, the closer the R^2 is to 1, the higher the goodness of fit, and the closer the predictive value is to the actual one, on the whole. The smaller s is, the smaller the mean deviation between the predictive value and the actual one. Generally, a consistent result will be presented from these two statistical parameters.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

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Author contributions

G.Y. initiated the project, hypothesis and design, analyzed the data and obtained regression equations, wrote the manuscript text, took part in the search and collection of flavonoids data, and prepared the figures and tables; X.X. and Y.G. performed the search and collection of flavonoids data, and took part in the preparation of figures and tables; H.Y., S.L., Y.S. and S.C. took part in the data processing and analysis. All authors reviewed the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Additional Information

Competing Interests: The author declare that they have no competing interests.

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Figures

Figure 1

(Author titled this "Figure 1") Diagram for the antibacterial activities and mechanisms of plant flavonoids to gram-positive bacteria.

Figure 2

(Author also titled this "Figure 1") Polynomial regression analyses for the physicochemical parameter LogP or LogD_{7.40} (x) and the MIC (y) to gram-positive bacteria mainly including *Staphylococcus aureus*, *S. epidermidis*, or/and *Bacillus subtilis*, of ninety-two plant flavonoids.

Figure 3

(Author titled this "Figure 2") Polynomial regression analyses for the physicochemical parameter LogP or LogD_{7.40} (x) and the $\log_{10}(\text{MIC})$ (y) to gram-positive bacteria, of ninety-two plant flavonoids.