

Bioactive chemical composition of cannabis extracts and cannabinoid receptors

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Table S1. LLD and LLQ values for the phytocannabinoids quantified in this study.

Phytocannabinoid	LLD (ng/ml)	LLQ (ng/ml)
Δ^9 -THC	0.53 – 29.43	1.90 – 32.66
Δ^9 -THCA	0.28 – 6.30	0.83 – 8.03
CBD	0.10 – 9.96	2.43 – 15.38
CBDA	0.62 – 7.59	1.17 – 9.04

Table S2. Categorization of data prior to regression analysis.

Independent Variables: Cannabinoid Concentration (% w/w or % w/v or % w/w ² or % w/v ²)				Dependent Variable: Receptor Potency (nM)		
				Sample Type	Receptor Subtype	Assay Mode
CBD	THC	CBDA	THCA	Cannabis Extracts	CB ₁	Agonism
						Antagonism
Or	Or	Or	Or		CB ₂	Agonism
						Antagonism
CBD ²	THC ²	CBDA ²	THCA ²	Cannabis Oil	CB ₁	Agonism
						Antagonism
					CB ₂	Agonism
						Antagonism

Table S3: Preliminary prediction models generated using all combinations of linear and quadratic explanatory variables, describing the relationship between chemical composition and potency at CB₂ as agonists for extracts obtained from dried plant samples. The model chosen as Equation 1 is underlined.

Model #	Equation	r ²	RMSE	Q ²
1	<u>$\text{Log}(EC_{50}) = -2.782 \text{ CBD} - 1.546 * 10^{-2} \text{ THC} + 4.823 * 10^{-3} \text{ CBDA} + 1.004 * 10^{-2} \text{ THCA} + 3.664$</u>	0.841	0.339	0.786
2	$\text{Log}(EC_{50}) = -2.779 \text{ CBD} - 1.545 * 10^{-2} \text{ THC} + 8.449 * 10^{-5} \text{ CBDA}^2 + 1.003 * 10^{-2} \text{ THCA} + 3.673$	0.837	0.343	0.783
<u>3</u>	<u>$\text{Log}(EC_{50}) = -2.967 \text{ CBD} - 1.649 * 10^{-2} \text{ THC} + 5.143 * 10^{-3} \text{ CBDA} + 1.363 * 10^{-4} \text{ THCA}^2 + 3.765$</u>	0.842	0.338	0.784
4	$\text{Log}(EC_{50}) = -2.957 \text{ CBD} - 1.644 * 10^{-2} \text{ THC} + 8.990 * 10^{-5} \text{ CBDA}^2 + 1.359 * 10^{-4} \text{ THCA}^2 + 3.775$	0.836	0.344	0.779
5	$\text{Log}(EC_{50}) = -2.765 \text{ CBD} - 3.039 * 10^{-4} \text{ THC}^2 + 4.794 * 10^{-3} \text{ CBDA} + 9.982 * 10^{-3} \text{ THCA} + 3.656$	0.820	0.360	0.754
6	$\text{Log}(EC_{50}) = -2.763 \text{ CBD} - 3.036 * 10^{-4} \text{ THC}^2 + 8.398 * 10^{-5} \text{ CBDA}^2 + 9.973 * 10^{-3} \text{ THCA} + 3.666$	0.817	0.364	0.752
7	$\text{Log}(EC_{50}) = -2.943 \text{ CBD} - 3.234 * 10^{-4} \text{ THC}^2 + 5.102 * 10^{-3} \text{ CBDA} + 1.352 * 10^{-4} \text{ THCA}^2 + 3.756$	0.819	0.361	0.749
8	$\text{Log}(EC_{50}) = -2.933 \text{ CBD} - 3.224 * 10^{-4} \text{ THC}^2 + 8.917 * 10^{-5} \text{ CBDA}^2 + 1.348 * 10^{-4} \text{ THCA}^2 + 3.767$	0.814	0.367	0.746
9	$\text{Log}(EC_{50}) = -9.420 \text{ CBD}^2 - 1.546 * 10^{-2} \text{ THC} + 4.823 * 10^{-3} \text{ CBDA} + 1.004 * 10^{-2} \text{ THCA} + 3.663$	0.838	0.342	0.783
10	$\text{Log}(EC_{50}) = -9.411 \text{ CBD}^2 - 1.545 * 10^{-2} \text{ THC} + 8.450 * 10^{-5} \text{ CBDA}^2 + 1.003 * 10^{-2} \text{ THCA} + 3.673$	0.834	0.346	0.779
11	$\text{Log}(EC_{50}) = -10.045 \text{ CBD}^2 - 1.649 * 10^{-2} \text{ THC} + 5.143 * 10^{-3} \text{ CBDA} + 1.363 * 10^{-4} \text{ THCA}^2 + 3.764$	0.839	0.341	0.780
12	$\text{Log}(EC_{50}) = -10.012 \text{ CBD}^2 - 1.644 * 10^{-2} \text{ THC} + 8.990 * 10^{-5} \text{ CBDA}^2 + 1.359 * 10^{-4} \text{ THCA}^2 + 3.774$	0.833	0.347	0.776
13	$\text{Log}(EC_{50}) = -9.355 \text{ CBD}^2 - 3.037 * 10^{-4} \text{ THC}^2 + 4.790 * 10^{-3} \text{ CBDA} + 9.974 * 10^{-3} \text{ THCA} + 3.656$	0.817	0.364	0.749
14	$\text{Log}(EC_{50}) = -9.345 \text{ CBD}^2 - 3.034 * 10^{-4} \text{ THC}^2 + 8.391 * 10^{-5} \text{ CBDA}^2 + 9.964 * 10^{-3} \text{ THCA} + 3.665$	0.813	0.367	0.747
15	$\text{Log}(EC_{50}) = -9.954 \text{ CBD}^2 - 3.231 * 10^{-4} \text{ THC}^2 + 5.096 * 10^{-3} \text{ CBDA} + 1.351 * 10^{-4} \text{ THCA}^2 + 3.756$	0.816	0.365	0.743
16	$\text{Log}(EC_{50}) = -9.921 \text{ CBD}^2 - 3.220 * 10^{-4} \text{ THC}^2 + 8.908 * 10^{-5} \text{ CBDA}^2 + 1.346 * 10^{-4} \text{ THCA}^2 + 3.766$	0.810	0.371	0.741

Table S4: Preliminary prediction models generated using all combinations of linear and quadratic explanatory variables, describing the relationship between chemical composition and potency at CB₁ as agonists for cannabis-derivative samples. The model chosen as Equation 2 is underlined.

Model #	Equation	r ²	RMSE	Q ²
1	$\text{Log}(EC_{50}) = 4.561 * 10^{-2} \text{ CBD} + 3.272 * 10^{-2} \text{ THC} + 4.849 * 10^{-3} \text{ CBDA} + 1.089 * 10^{-2} \text{ THCA} + 1.795$	0.264	0.394	-0.002
2	$\text{Log}(EC_{50}) = 4.484 * 10^{-2} \text{ CBD} + 3.217 * 10^{-2} \text{ THC} + 1.628 * 10^{-4} \text{ CBDA}^2 + 1.071 * 10^{-2} \text{ THCA} + 1.798$	0.263	0.394	-0.015
3	$\text{Log}(EC_{50}) = 4.559 * 10^{-2} \text{ CBD} + 3.271 * 10^{-2} \text{ THC} + 4.847 * 10^{-3} \text{ CBDA} + 7.122 * 10^{-4} \text{ THCA}^2 + 1.795$	0.264	0.394	-0.003
4	$\text{Log}(EC_{50}) = 4.482 * 10^{-2} \text{ CBD} + 3.215 * 10^{-2} \text{ THC} + 1.627 * 10^{-4} \text{ CBDA}^2 + 7.001 * 10^{-4} \text{ THCA}^2 + 1.798$	0.263	0.394	-0.015
<u>5</u>	$\text{Log}(EC_{50}) = 1.421 * 10^{-1} \text{ CBD} + 5.089 * 10^{-2} \text{ THC}^2 - 2.356 * 10^{-2} \text{ CBDA} - 3.833 * 10^{-2} \text{ THCA} + 1.510$	0.679	0.260	0.304
6	$\text{Log}(EC_{50}) = 1.404 * 10^{-1} \text{ CBD} + 5.008 * 10^{-2} \text{ THC}^2 - 6.453 * 10^{-4} \text{ CBDA}^2 - 4.222 * 10^{-2} \text{ THCA} + 1.511$	0.664	0.266	0.211
7	$\text{Log}(EC_{50}) = 1.420 * 10^{-1} \text{ CBD} + 5.088 * 10^{-2} \text{ THC}^2 - 2.362 * 10^{-2} \text{ CBDA} - 2.492 * 10^{-3} \text{ THCA}^2 + 1.510$	0.679	0.260	0.303
8	$\text{Log}(EC_{50}) = 4.214 * 10^{-2} \text{ CBD} + 9.443 * 10^{-3} \text{ THC}^2 + 1.529 * 10^{-4} \text{ CBDA}^2 + 6.582 * 10^{-4} \text{ THCA}^2 + 1.806$	0.275	0.391	-0.082
9	$\text{Log}(EC_{50}) = 5.424 * 10^{-3} \text{ CBD}^2 + 3.327 * 10^{-2} \text{ THC} + 4.931 * 10^{-3} \text{ CBDA} + 1.107 * 10^{-2} \text{ THCA} + 1.829$	0.285	0.389	0.045
10	$\text{Log}(EC_{50}) = 5.330 * 10^{-3} \text{ CBD}^2 + 3.270 * 10^{-2} \text{ THC} + 1.654 * 10^{-4} \text{ CBDA}^2 + 1.088 * 10^{-2} \text{ THCA} + 1.831$	0.284	0.389	0.036
11	$\text{Log}(EC_{50}) = 5.421 * 10^{-3} \text{ CBD}^2 + 3.326 * 10^{-2} \text{ THC} + 4.929 * 10^{-3} \text{ CBDA} + 7.242 * 10^{-4} \text{ THCA}^2 + 1.829$	0.285	0.389	0.044
12	$\text{Log}(EC_{50}) = 5.328 * 10^{-3} \text{ CBD}^2 + 3.268 * 10^{-2} \text{ THC} + 1.654 * 10^{-4} \text{ CBDA}^2 + 7.117 * 10^{-4} \text{ THCA}^2 + 1.831$	0.284	0.389	0.036
13	$\text{Log}(EC_{50}) = 1.339 * 10^{-2} \text{ CBD}^2 + 1.440 * 10^{-2} \text{ THC}^2 - 8.086 * 10^{-3} \text{ CBDA} - 1.306 * 10^{-2} \text{ THCA} + 1.752$	0.525	0.317	0.204
14	$\text{Log}(EC_{50}) = 1.323 * 10^{-2} \text{ CBD}^2 + 1.385 * 10^{-2} \text{ THC}^2 - 2.128 * 10^{-4} \text{ CBDA}^2 - 1.392 * 10^{-2} \text{ THCA} + 1.753$	0.517	0.319	0.172
15	$\text{Log}(EC_{50}) = 1.339 * 10^{-2} \text{ CBD}^2 + 1.439 * 10^{-2} \text{ THC}^2 - 8.098 * 10^{-3} \text{ CBDA} - 8.481 * 10^{-4} \text{ THCA}^2 + 1.752$	0.525	0.317	0.203

16	$\text{Log}(EC_{50}) = 1.323 * 10^{-2} CBD^2 + 1.384 * 10^{-2} THC^2 - 2.131 * 10^{-4} CBDA^2 - 9.039 * 10^{-4} THCA^2 + 1.753$	0.517	0.319	0.171
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Table S5: Preliminary prediction models generated using all combinations of linear and quadratic explanatory variables, describing the relationship between chemical composition and potency at CB₁ as agonists for extracts obtained from dried plant samples. The model chosen as Equation 3 is underlined.

Model #	Equation	r ²	RMSE	Q ²
1	<u>$\text{Log}(EC_{50}) = 5.435 * 10^{-3} \text{ CBD} - 6.101 * 10^{-3} \text{ THC} + 4.938 * 10^{-3} \text{ CBDA} + 5.834 * 10^{-3} \text{ THCA} + 2.682$</u>	0.196	0.601	0.125
2	$\text{Log}(EC_{50}) = 5.479 * 10^{-3} \text{ CBD} - 6.151 * 10^{-3} \text{ THC} + 1.085 * 10^{-3} \text{ CBDA}^2 + 5.882 * 10^{-3} \text{ THCA} + 2.681$	0.204	0.598	0.140
3	<u>$\text{Log}(EC_{50}) = 5.690 * 10^{-3} \text{ CBD} - 6.388 * 10^{-3} \text{ THC} + 5.171 * 10^{-3} \text{ CBDA} + 8.740 * 10^{-5} \text{ THCA}^2 + 2.699$</u>	0.194	0.602	0.119
4	$\text{Log}(EC_{50}) = 5.722 * 10^{-3} \text{ CBD} - 6.423 * 10^{-3} \text{ THC} + 1.133 * 10^{-4} \text{ CBDA}^2 + 8.788 * 10^{-5} \text{ THCA}^2 + 2.698$	0.202	0.599	0.134
5	$\text{Log}(EC_{50}) = 6.157 * 10^{-3} \text{ CBD} - 8.791 * 10^{-5} \text{ THC}^2 + 5.594 * 10^{-3} \text{ CBDA} + 6.609 * 10^{-3} \text{ THCA} + 2.615$	0.187	0.605	0.105
6	$\text{Log}(EC_{50}) = 6.225 * 10^{-3} \text{ CBD} - 8.889 * 10^{-5} \text{ THC}^2 + 1.233 * 10^{-4} \text{ CBDA}^2 + 6.683 * 10^{-3} \text{ THCA} + 2.613$	0.196	0.601	0.122
7	$\text{Log}(EC_{50}) = 6.438 * 10^{-3} \text{ CBD} - 9.193 * 10^{-5} \text{ THC}^2 + 5.850 * 10^{-3} \text{ CBDA} + 9.888 * 10^{-5} \text{ THCA}^2 + 2.631$	0.183	0.606	0.096
8	$\text{Log}(EC_{50}) = 6.489 * 10^{-3} \text{ CBD} - 9.265 * 10^{-5} \text{ THC}^2 + 1.285 * 10^{-4} \text{ CBDA}^2 + 9.966 * 10^{-5} \text{ THCA}^2 + 2.629$	0.192	0.603	0.113
9	$\text{Log}(EC_{50}) = 9.093 * 10^{-5} \text{ CBD}^2 - 5.939 * 10^{-3} \text{ THC} + 4.807 * 10^{-3} \text{ CBDA} + 5.680 * 10^{-3} \text{ THCA} + 2.692$	0.183	0.606	0.129
10	$\text{Log}(EC_{50}) = 9.175 * 10^{-5} \text{ CBD}^2 - 5.993 * 10^{-3} \text{ THC} + 1.057 * 10^{-4} \text{ CBDA}^2 + 5.730 * 10^{-3} \text{ THCA} + 2.691$	0.191	0.603	0.144
11	$\text{Log}(EC_{50}) = 9.552 * 10^{-5} \text{ CBD}^2 - 6.239 * 10^{-3} \text{ THC} + 5.050 * 10^{-3} \text{ CBDA} + 8.536 * 10^{-5} \text{ THCA}^2 + 2.709$	0.181	0.607	0.124
12	$\text{Log}(EC_{50}) = 9.610 * 10^{-5} \text{ CBD}^2 - 6.277 * 10^{-3} \text{ THC} + 1.107 * 10^{-4} \text{ CBDA}^2 + 8.588 * 10^{-5} \text{ THCA}^2 + 2.708$	0.189	0.604	0.139
13	$\text{Log}(EC_{50}) = 1.026 * 10^{-4} \text{ CBD}^2 - 8.525 * 10^{-5} \text{ THC}^2 + 5.425 * 10^{-3} \text{ CBDA} + 6.409 * 10^{-3} \text{ THCA} + 2.628$	0.172	0.610	0.109
14	$\text{Log}(EC_{50}) = 1.039 * 10^{-4} \text{ CBD}^2 - 8.629 * 10^{-5} \text{ THC}^2 + 1.197 * 10^{-4} \text{ CBDA}^2 + 6.487 * 10^{-3} \text{ THCA} + 2.627$	0.182	0.606	0.126
15	$\text{Log}(EC_{50}) = 1.078 * 10^{-4} \text{ CBD}^2 - 8.954 * 10^{-5} \text{ THC}^2 + 5.698 * 10^{-3} \text{ CBDA} + 9.631 * 10^{-5} \text{ THCA}^2 + 2.644$	0.169	0.611	0.102

16	$\text{Log}(EC_{50}) = 1.087 * 10^{-4} \text{ CBD}^2 - 9.032 * 10^{-5} \text{ THC}^2 + 1.253 * 10^{-4} \text{ CBDA}^2 + 9.716 * 10^{-5} \text{ THCA}^2 + 2.643$	0.178	0.608	0.119
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Figure S1. Dose-response curves for (A) CBD and CBDA, and (C) Δ^9 -THC and Δ^9 -THCA [Ref. 15] as agonists at CB₁ receptor, using CP-55940 as a reference compound. Panels (B) and (D) show the dose-response curves for CBD and CBDA, and Δ^9 -THC and Δ^9 -THCA as antagonists, respectively, with SR-141716 as a reference compound at CB₁ receptor.

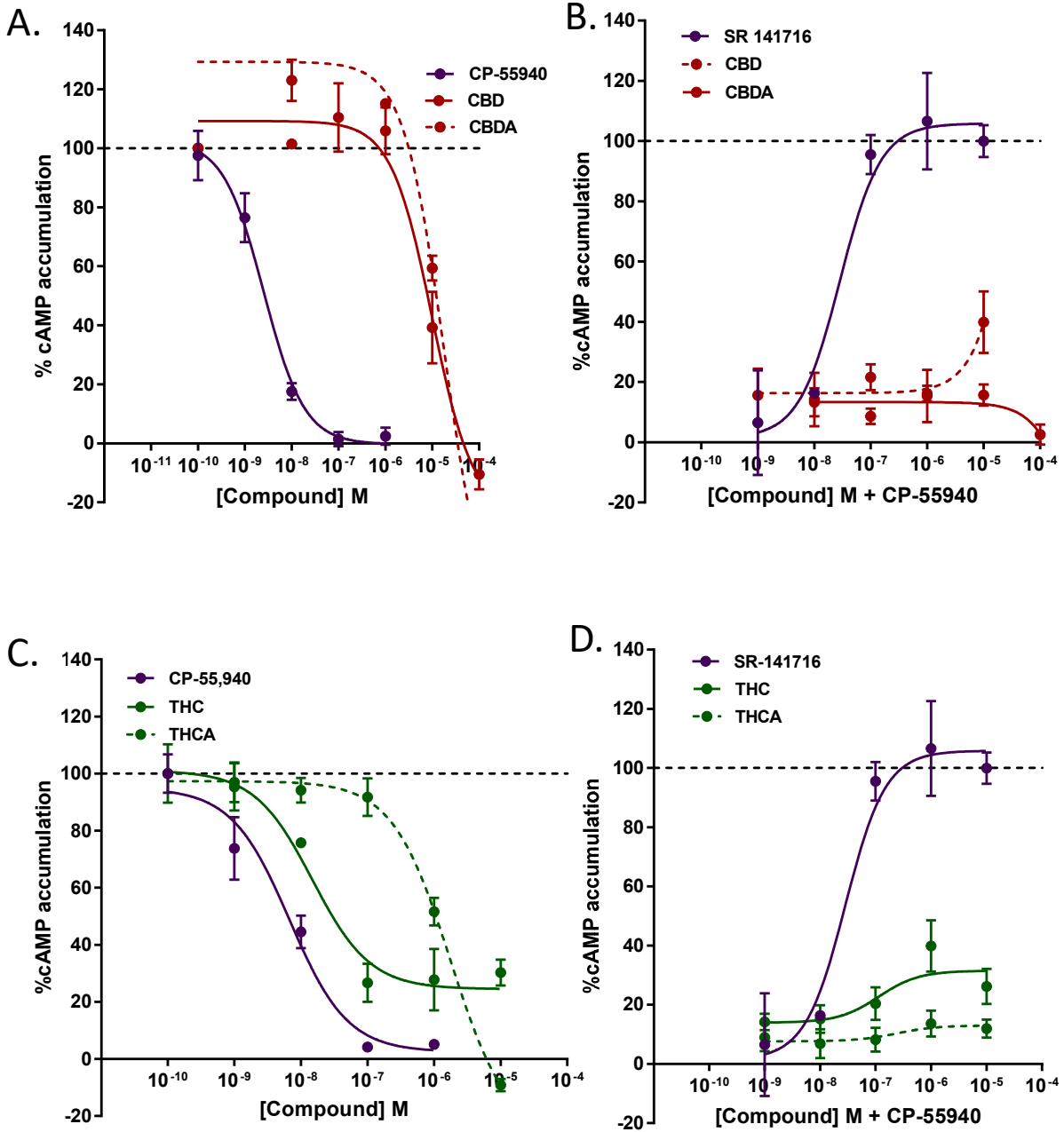


Figure S2. Dose-response curves for (A) CBD and CBDA, and (C) Δ^9 -THC and Δ^9 -THCA as agonists at CB₂ receptor, using CP-55940 as a reference compound. Panels (B) [Ref. 15] and (D) show the dose-response curves for CBD and CBDA, and Δ^9 -THC and Δ^9 -THCA as antagonists, respectively, with AM630 as a reference compound at CB₂ receptor.

