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Table S1. Protein Data Bank (PDB) identifiers, central grid values and resolutions of enzymes used in the study

Enzyme	PDB ID	Centre grid (X, Y, Z)/Å	Resolution (X-ray diffraction)/Å	Exhaustiveness
α-amylase	3bc9	47.788286, 25.075619, 5.722952	1.35	100
α-glucosidase	1obb	30.179130, 33.953391, 22.922000	1.90	100

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Table S2. Absorption and distribution properties of phytochemicals from the leaf extract of *Coccinia grandis* to assess their likely permeability and bioavailability across different physiological barriers

Phytochemical	HIA	Caco-2 permeability	BBBP	P-glycoprotein inhibitor	P-glycoprotein substrate	MDCK permeability	$F_{20\,\%}$	$F_{30\,\%}$	PPB/%	VD	Fu/%
Benzofuranone	0.006	-4.594	0.239	0.001	0.255	2.2e-05	0.888	0.906	92.28	0.849	10.170
Campesterol	0.004	-4.740	0.854	0.377	0.001	9e-06	0.013	0.243	98.61	1.842	1.789
Campocatechin	0.004	-4.930	0.529	0.013	0.005	2.7e-05	0.002	0.003	90.80	0.525	3.310
Coniferyl alcohol	0.010	-4.457	0.295	0.001	0.321	1.8e-05	0.005	0.742	80.73	1.059	16.950
Ethisterone	0.008	-4.725	0.964	0.104	0.000	2.1e-05	0.553	0.004	95.28	1.034	1.424
Ferulic acid	0.030	-4.902	0.329	0.000	0.086	1.5e-05	0.047	0.584	89.75	0.339	6.394
Furanone	0.006	-4.446	0.219	0.000	0.022	2.2e-05	0.015	0.008	79.21	2.455	38.780
Isosteviol	0.006	-5.285	0.221	0.009	0.000	1.7e-05	0.002	0.890	91.25	0.558	9.029
Kaempferol	0.008	-4.974	0.009	0.004	0.001	9e-06	0.856	0.993	97.86	0.522	4.411
Luteolin	0.047	-5.028	0.009	0.004	0.274	1e-05	0.998	1.000	95.43	0.533	5.984
Methyl caffeate	0.020	-4.631	0.185	0.001	0.077	2e-05	0.025	0.806	85.83	0.390	10.410
p-coumaric acid	0.009	-4.961	0.290	0.000	0.017	1.3e-05	0.004	0.194	85.36	0.293	13.720
Quercetin	0.014	-5.204	0.008	0.004	0.005	8e-06	0.930	0.997	95.49	0.579	7.423
Listroside	0.927	-5.702	0.596	0.000	0.673	0.000102	0.100	0.998	63.72	0.394	34.460
Lukianol	0.007	-4.744	0.010	0.048	0.006	1.3e-05	0.943	0.537	101.10	0.414	0.795
Oleuropein	0.950	-5.847	0.672	0.000	0.842	0.000103	0.371	0.998	74.00	0.568	25.640
Sinapic acid	0.165	-4.962	0.271	0.001	0.040	1.3e-05	0.189	0.624	88.79	0.450	9.389
Stigmasterol	0.005	-4.668	0.691	0.066	0.001	8e-06	0.008	0.185	98.67	2.408	1.572
Undecanol	0.003	-4.414	0.890	0.004	0.012	2.2e-05	0.261	0.979	93.51	1.628	5.165

HIA=human intestinal absorption: category 1=HIA+(HIA <30 %), category 0=HIA-(HIA <30 %). Caco-2 permeability: optimal=higher than –5.15 log cm/s. BBBP=blood-brain barrier penetration: category 1=BBB+, category 0=BBB-. P-glycoprotein inhibitor: category 1=inhibitor, category 0=non-inhibitor. P-glycoprotein substrate: category 1=substrate, category 0=non-substrate. MDCK permeability=Madin–Darby canine kidney cells: low permeability: $<2{\cdot}10^{-6}$ cm/s, medium permeability: 2 to $20{\cdot}10^{-6}$ cm/s, high passive permeability: $>20{\cdot}10^{-6}$ cm/s. $F_{20\,\%}$=20 % bioavailability: category 1=$F_{20\,\%}$+ (bioavailability <20 %), category 0=$F_{20\,\%}$– (bioavailability ≥20 %). $F_{30\,\%}$=30 % bioavailability: category 1=$F_{30\,\%}$+ (bioavailability <30 %), category 0=$F_{30\,\%}$– (bioavailability ≥30 %). PPB=plasma protein binding: optimal <90 %. Highly protein-bound drugs may have a low therapeutic index. VD=volume distribution: optimal=0.04–20 L/kg. Fu=fraction unbound: in plasma, low <5 %, medium 5–20 %, high >20 %. The output value is the probability of being within the range of 0 to 1

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Table S3. The metabolic profile of phytochemicals from *Coccinia grandis* leaf extract with different substrates and inhibitors of the cytochrome P450 enzyme family

Phytochemical	CYP1A2 inhibitor	CYP1A2 substrate	CYP2C19 inhibitor	CYP2C19 substrate	CYP2C9 inhibitor	CYP2C9 substrate	CYP2D6 inhibitor	CYP2D6 substrate	CYP3A4 inhibitor	CYP3A4 substrate
Benzofuranone	0.914	1.716	0.156	0.091	0.044	0.776	0.161	0.774	0.018	0.215
Campesterol	0.055	0.523	0.071	0.957	0.093	0.216	0.005	0.445	0.181	0.769
Campocatechin	0.928	0.767	0.629	0.346	0.554	0.429	0.054	0.458	0.298	0.419
Coniferyl alcohol	0.709	0.867	0.042	0.422	0.032	0.836	0.019	0.893	0.087	0.241
Ethisterone	0.107	0.846	0.891	0.93	0.445	0.23	0.093	0.142	0.639	0.93
Ferulic acid	0.059	0.478	0.042	0.057	0.142	0.367	0.02	0.199	0.026	0.075
Furanone	0.205	0.147	0.048	0.072	0.014	0.399	0.018	0.597	0.008	0.179
Isosteviol	0.005	0.855	0.016	0.901	0.089	0.254	0.007	0.157	0.26	0.078
Kaempferol	0.972	0.11	0.181	0.046	0.653	0.867	0.722	0.283	0.697	0.08
Luteolin	0.981	0.154	0.124	0.046	0.576	0.842	0.568	0.559	0.549	0.092
Methyl caffeate	0.899	0.696	0.252	0.078	0.436	0.86	0.164	0.732	0.292	0.227
p-coumaric acid	0.061	0.067	0.046	0.052	0.232	0.566	0.019	0.169	0.031	0.08
Quercetin	0.943	0.115	0.053	0.041	0.598	0.643	0.411	0.205	0.348	0.046
Listroside	0.014	0.077	0.045	0.204	0.016	0.145	0.012	0.084	0.21	0.2
Lukianol	0.885	0.104	0.769	0.043	0.491	0.889	0.289	0.871	0.308	0.23
Oleuropein	0.017	0.071	0.035	0.071	0.014	0.582	0.003	0.12	0.357	0.157
Sinapic acid	0.046	0.833	0.026	0.063	0.053	0.277	0.016	0.198	0.01	0.084
stigmasterol	0.041	0.603	0.074	0.954	0.106	0.132	0.038	0.643	0.339	0.852
Undecanol	0.905	0.319	0.401	0.07	0.281	0.865	0.01	0.077	0.058	0.074

Obtained values provide information on the specific metabolic pathways and interactions involved in the biotransformation of the phytochemicals. The output value is the probability of being substrate/inhibitor, within the range of 0 (no effect) to 1 (high effect)

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Table S4. Toxicological effects of phytochemicals from *Coccinia grandis* on the human body based on different toxicity tests

Phytochemical	hERG blocker	Hepato-toxicity	DILI	Ames toxicity	Rat oral acute toxicity	FDAMDD	Skin sensiti-sation	Carcino-genicity	Eye corro-sion	Eye irritation	Respi-ratory toxicity
Benzofuranone	0.013	0.582	0.582	0.266	0.422	0.032	0.391	0.835	0.742	0.991	0.638
Campesterol	0.04	0.193	0281	0.032	0.023	0.645	0.176	0.067	0.003	0.01	0.502
Campocatechin	0.162	0.753	0.414	0.744	0.876	0.908	0.04	0.562	0.003	0.014	0.036
Coniferyl alcohol	0.035	0.17	0.045	0.141	0.386	0.09	0.949	0.662	0.493	0.987	0.502
Ethisterone	0.041	0.149	0.18	0.015	0.163	0.884	0.032	0.916	0.004	0.023	0.961
Ferulic acid	0.023	0.345	0.511	0.114	0.733	0.076	0.929	0.443	0.515	0.979	0.72
Furanone	0.02	0.13	0.126	0.071	0.877	0.016	0.293	0.908	0.985	0.996	0.906
Isosteviol	0.002	0.422	0.027	0.033	0.082	0.132	0.012	0.102	0.004	0.507	0.949
Kaempferol	0.07	0.098	0.979	0.672	0.156	0.109	0.856	0.097	0.009	0.929	0.09
Luteolin	0.064	0.084	0.905	0.536	0.046	0.741	0.946	0.095	0.009	0.944	0.22
Methyl caffeate	0.034	0.244	0.082	0.375	0.801	0.234	0.94	0.392	0.046	0.461	0.448
p-coumaric acid	0.025	0.673	0.2	0.045	0.796	0.031	0.941	0.151	0.672	0.988	0.512
Quercetin	0.099	0.1	0.98	0.657	0.065	0.31	0.919	0.05	0.007	0.936	0.072
Listroside	0.005	0.168	0.954	0.693	0.088	0.147	0.032	0.954	0.003	0.007	0.643
Lukianol	0.106	0.25	0.976	0.012	0.1	0.385	0.206	0.099	0.003	0.106	0.064
Oleuropein	0.003	0.127	0.954	0.781	0.136	0.2	0.028	0.953	0.003	0.007	0.72
Sinapic acid	0.018	0.363	0.21	0.016	0.321	0.055	0.949	0.278	0.391	0.94	0.428
Stigmasterol	0.012	0.011	0.055	0.029	0.054	0.539	0.025	0.054	0.003	0.001	0.19
Undecanol	0.106	0.016	0.04	0.007	0.041	0.013	0.926	0.066	0.991	0.971	0.341

hERG=human ether-a-go-go related gene, DILI=drug-induced liver injury, FDAMDD=Food and Drug Administration recommended maximum daily drug dose. All values are between 0 and 1, with 0 indicating that there is no effect and 1 that there is a high effect

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Table S5. Mechanism for predicting the toxicity of *Coccinia grandis* leaf extract using the Tox21 pathway to evaluate the effects of phytochemicals on both nuclear and stress response pathways

Phytochemical	NR-AR	NR-AR-LBD	NR-AhR	NR-aromatase	NR-ER	NR-ER-LBD	NR-PPAR-γ	SR-ARE	SR-ATAD5	SR-HSE	SR-MMP	SR-p53
Benzofuranone	0.013	0.005	0.375	0.01	0.29	0.008	0.004	0.528	0.016	0.06	0.346	0.067
Campesterol	0.002	0.003	0.0	0.012	0.397	0.933	0.008	0.123	0.001	0.046	0.89	0.014
Campocatechin	0.027	0.626	0.625	0.905	0.489	0.256	0.808	0.86	0.6	0.715	0.851	0.97
Coniferyl alcohol	0.033	0.014	0.613	0.08	0.152	0.011	0.011	0.482	0.176	0.239	0.317	0.422
Ethisterone	0.765	0.919	0.005	0.589	0.671	0.865	0.563	0.699	0.045	0.588	0.965	0.855
Ferulic acid	0.809	0.278	0.277	0.021	0.254	0.033	0.07	0.525	0.19	0.296	0.22	0.171
Furanone	0.029	0.003	0.017	0.004	0.168	0.006	0.002	0.073	0.006	0.019	0.023	0.005
Isosteviol	0.265	0.044	0.003	0.578	0.132	0.061	0.858	0.135	0.045	0.239	0.571	0.091
Kaempferol	0.008	0.371	0.967	0.941	0.959	0.985	0.963	0.873	0.612	0.557	0.968	0.921
Luteolin	0.079	0.169	0.977	0.908	0.954	0.996	0.939	0.884	0.675	0.888	0.976	0.891
Methyl caffeate	0.735	0.655	0.912	0.195	0.572	0.855	0.375	0.905	0.8	0.892	0.827	0.796
p-coumaric acid	0.857	0.349	0.229	0.011	0.477	0.432	0.012	0.783	0.153	0.237	0.318	0.347
Quercetin	0.01	0.179	0.967	0.917	0.927	0.987	0.961	0.815	0.436	0.655	0.962	0.888
Listroside	0.006	0.241	0.035	0.032	0.186	0.013	0.048	0.161	0.202	0.017	0.0715	0.44
Lukianol	0.078	0.567	0.915	0.965	0.981	0.996	0.975	0.948	0.706	0.482	0.989	0.93
Oleuropein	0.006	0.185	0.111	0.044	0.187	0.011	0.251	0.329	0.298	0.06	0.728	0.42
Sinapic acid	0.226	0.153	0.205	0.393	0.198	0.013	0.829	0.57	0.483	0.357	0.28	0.678
stigmasterol	0.0	0.002	0.0	0.005	0.369	0.923	0.005	0.135	0.001	0.052	0.943	0.015
Undecanol	0.016	0.002	0.006	0.041	0.0288	0.017	0.04	0.066	0.004	0.519	0.051	0.031

NR-AR=nuclear-hormone receptor, androgen receptor, NR-AR-LBD=nuclear-hormone receptor, androgen receptor-ligand binding domain, NR-AhR=nuclear-hormone receptor-aryl hydrocarbon receptor, NR-ER=nuclear hormone receptor-estrogen receptor, NR-ER-LBD=nuclear hormone receptor-estrogen receptor ligand-binding domain, NR-PPAR-γ=nuclear hormo ne-peroxisome proliferator-activated receptor gamma, SR-ARE=antioxidant response element, SR-ATAD5=ATPase family AAA domain-containing protein 5, SR-HSE=heat shock factor response element, SR-MMP=mitochondrial membrane potential, SR-p53. All the values are between 0 and 1, with 0 indicating that there is no effect and 1 that there is a high effect

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Table S6. Results of the process of elimination and investigation of the harmful effects of phytochemicals from *Coccinia grandis* on the external environment to understand their excretion dynamics and environmental toxicology

Phytochemical	Clearance/(mL/(min·kg)	$t_{1/2}$	BCF/log10 (L/kg)	IC_{50}	LC_{50}	
					PP	DM
Benzofuranone	11.101	0.83	0.718	2.999	3.449	4.352
Campesterol	17.948	0.0015	3.141	4.855	4.972	5.897
Campocatechin	6.862	0.332	1.379	4.15	6.075	5.553
Coniferyl alcohol	12.341	0.92	0.707	2.958	3.625	3.913
Ethisterone	5.594	0.208	0.559	2.81	2.71	4.556
Ferulic acid	7.48	0.926	0.454	3.086	3.249	3.908
Furanone	14.22	0.894	0.522	2.235	2.799	3.76
Isosteviol	0.344	0.503	0.212	3.28	3.215	4.207
Kaempferol	6.868	0.905	0.986	4.386	5.223	5.205
Luteolin	8.146	0.898	1.016	4.432	5.222	5.302
Methyl caffeate	15.624	0.93	0.657	3.886	0.047	4.92
p-coumaric acid	6.299	0.919	0.416	3.136	3.373	3.775
Quercetin	8.284	0.929	1.017	4.231	5.222	5.331
Listroside	2.057	0.647	0.519	3.099	4.572	5.312
Lukianol	6.776	0.276	1.856	5.61	6.248	6.491
Oleuropein	2.585	0.832	0.556	3.52	4.591	5.383
Sinapic acid	7.776	0.933	0.472	2.765	3.002	3.951
stigmasterol	15.958	0.014	3.367	4.978	5.511	6.355
Undecanol	7.769	0.409	1.871	4.853	4.811	3.82

Clearance: high >15, moderate 5–15, low <5 mL/(min·kg); $t_{1/2}$=half-life: category 1=long half-life (>3 h), category 0=short half-life (<3 h). BCF=bioconcentration factors used for considering secondary poisoning potential and assessing risks to human health *via* the food chain. IC_{50}=50 % growth inhibitory concentration on *Tetrahymena pyriformis*, LC_{50}=50 % lethal concentration on *Pimephales promelas* (PP) and *Daphnia magna* (DM) after 96 and 48 h, respectively

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Table S7. Predicted and validated values of total phenolic content (TPC), total flavonoid content (TFC), total tannin content (TTC), 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity, and Fe(III) reducing antioxidant power (FRAP) expressed on dry mass basis obtained with the optimized conditions of microwave-assisted extraction of *Coccinia grandis* leaf extract

Parameter	Experimental value	RSM value	Relative error/%
TPC as *w*(GAE)/(mg/g)	79.86	81.87	2.4
TFC as *w*(QE)/(mg/g)	23.12	21.24	8.85
TTC as *w*(TAE)/(mg/g)	35.03	35.24	0.59
DPPH/%	83.62	85.83	2.5
FRAP as *w*(TE)/(mg/g)	101.56	102.27	0.69

RSM=response surface methodology, GAE=gallic acid equivalents, QE=quercetin equivalents, TAE=tannic acid equivalents, TE=Trolox equivalents

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Table S8. Identification of phytochemicals from *Coccinia grandis* leaf using liquid-chromatography-mass spectrometry analysis, their mass-to-charge ratios (*m/z*) and corresponding retention times (t_R)

Sample	Phytocompound	Molecular formula	Compound type	t_R/min	Parent ion (*m/z*)	Ionization mode
1	Benzofuranone	$C_8H_6O_2$	Furan	5.6	136.36	Negative
2	Camptothecin	$C_{20}H_{16}N_2O_4$	Quinoline	28.04	348.70	Negative
3	Campesterol	$C_{28}H_{48}O$	Sterol	32.02	400.7	Negative
4	Coniferyl alcohol	$C_{10}H_{12}O_3$	Alcohol	30.34	180.54	Negative
5	Ethisterone	$C_{10}H_{12}O_3$	Steroid	11.60	310.14	Negative
6	Ferulic acid	$C_{10}H_{10}O_4$	Cinnamic acid	12.63	194.63	Negative
7	Isosteviol	$C_{20}H_{30}O_3$	Terpenoid	39.58	316	Negative
8	Kaempferol	$C_{15}H_{10}O_6$	Flavonoid	15.10	286.16	Positive
9	Luteolin	$C_{15}H_{10}O_6$	Flavone	17.22	286.20	Positive
10	Methyl caffeate	$C_{10}H_{10}O_4$	Caffeate ester	14.67	194.70	Negative
11	*p*-coumaric acid	$C_9H_8O_3$	Coumarin	3.95	164.15	Positive
12	Sinapic acid	$C_{11}H_{12}O_5$	Cinnamic acid	20.34	224.71	Negative
13	Stigmasterol	$C_{29}H_{48}O$	Sterol	27.01	412.05	Negative
14	Undecanol	$C_{11}H_{24}O$	Alcohol	1.09	172.64	Negative
15	Isosteviol	$C_{20}H_{30}O_3$	Terpenoid	39.58	316	Negative
16	Kaempferol	$C_{15}H_{10}O_6$	Flavonoid	15.10	286.16	Positive

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Table S9. Inhibitory effect of *Coccinia grandis* extract at different concentrations on α-amylase, and its IC_{50} value

γ(extract)/(μg/mL)	α-amylase inhibition/%	
	Acarbose	*C. grandis*
125.0	56.4±2.4	70.8±1.2
62.5	53.3±3.4	52.6±0.7
31.2	42.7±3.2	46.3±2.0
15.6	33.7±1.8	43.1±1.1
7.8	26.7±2.5	30.3±0.8
IC_{50}/(μg/mL)	79.9±8.1	52.4±2.7

The results are expressed as mean value±standard deviation, N=3, $p<0.05$

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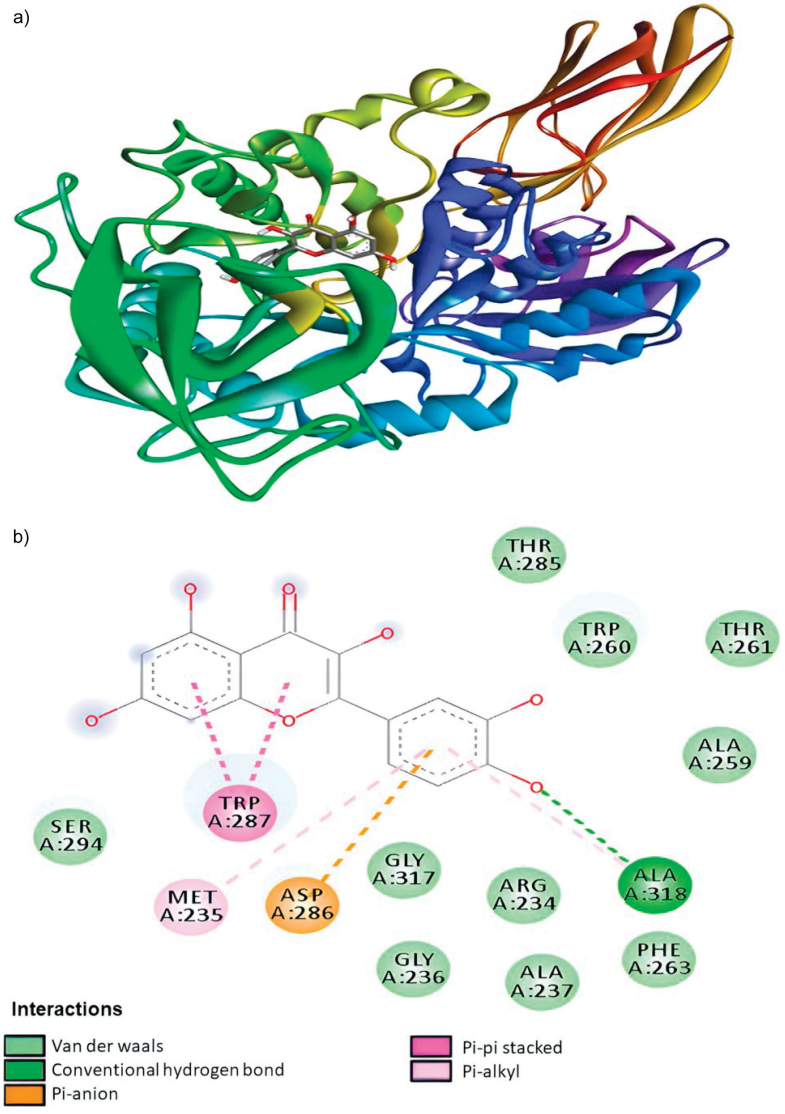

Fig. S1. Molecular interactions between an enzyme-phytochemical complex in *Coccinia grandis* leaf extract: a) three-dimensional ribbon structure of α-amylase interacting with quercetin shows the binding position at the active site of the α-amylase, including the specific amino acid residues involved in the interaction, and b) two-dimensional structure illustrates the different types of bonds formed between the enzyme and quercetin, together with their respective bond orders, which range from 2.54 to 5.00 Å. A=side chain of α-amylase enzyme

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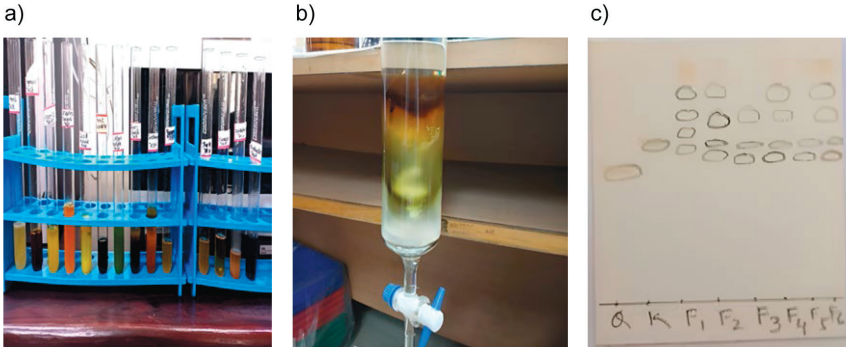

Fig. S2. Analysis of phytochemicals from *Coccinia grandis* leaf extract included three main steps: a) preliminary phytochemical screening, b) column chromatography, and c) identification of the presence of kaempferol by thin-layer chromatography

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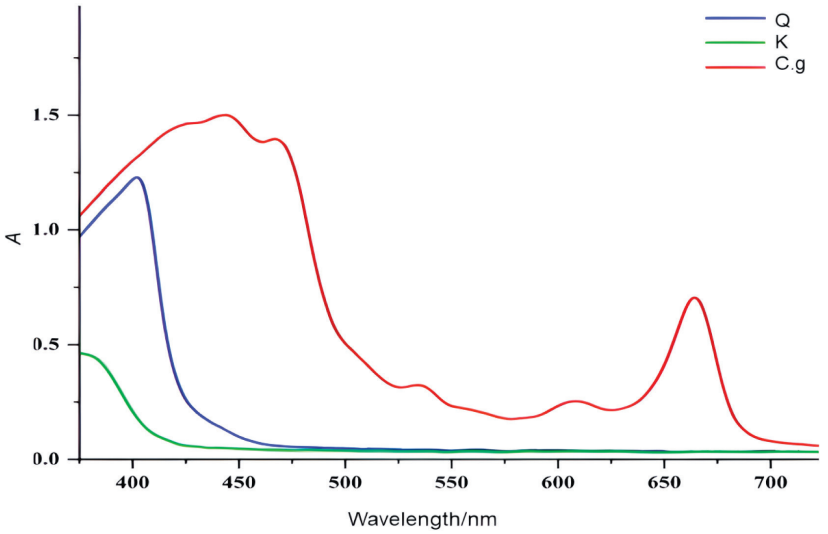

Fig. S3. Spectra for the presence of phenolic compounds and flavonoids in *Coccinia grandis* leaf extract using UV-visible spectral analysis. K=kaempferol, Q=quercetin, C.g=*Coccinia grandis*

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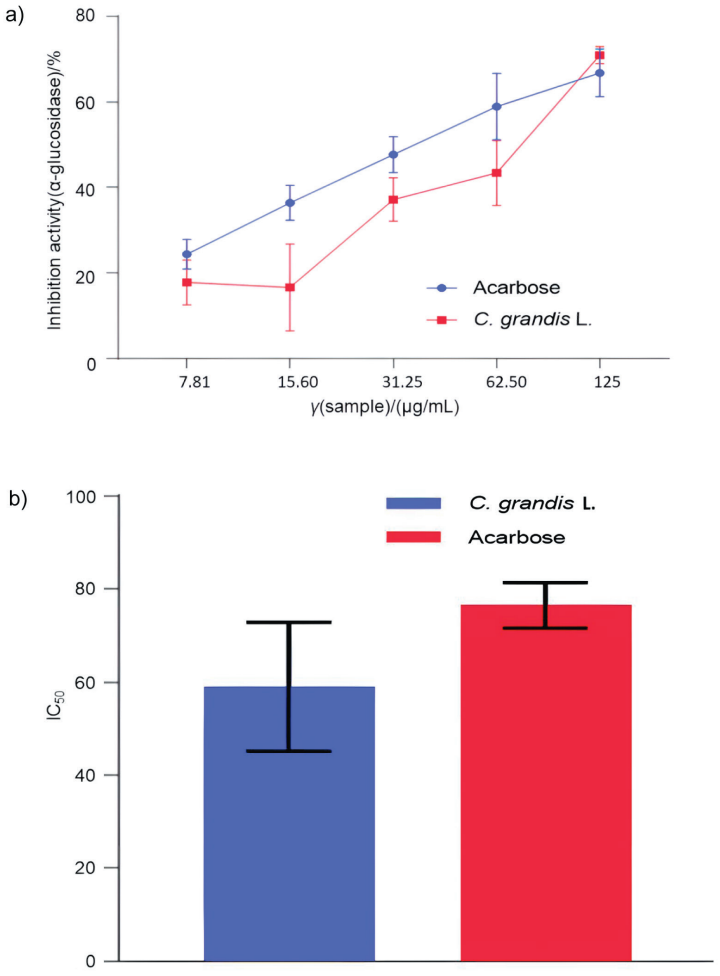

Fig. S4. Determination of inhibitory activity of *Coccinia grandis* leaf extract and acarbose on α-glucosidase: a) inhibition percentage (maximum value of (70.9±1.6) %) at different concentrations of the leaf extract, and b) its half maximal inhibitory concentration (IC_{50}=(76.5±4.0) μg/mL). All results are given as mean values of three experiments (*N*=3, $p<0.05$)