Table S1:

Gene symbol	Full name	Functional class	Primary source (Pathv	Secondary evidence (re	HGNC ID	Used in downstream analyses
ABCC8	ATP binding cassette subf	secretory layer	KEGG: hsa04911 (Insu	De Franco 2020, PMID:	59	Yes
GCG	glucagon	secretory layer	Reactome: R-HSA-381	Müller 2019, PMID: 317	4191	Yes
KCNJ11	potassium inwardly rectif	secretory layer	KEGG: hsa04911 (Insu	De Franco 2020, PMID:	6257	Yes
KCNQ1	potassium voltage-gated c	secretory layer	GO:0030073 (Insulin s	Yamagata 2011, PMID: 2	6294	Yes
PCSK1	proprotein convertase sul	secretory layer	Reactome: R-HSA-381	Müller 2019, PMID: 317	8743	Yes
SLC2A2	solute carrier family 2 me	secretory layer	KEGG: hsa04911 (Insu	—	11006	Yes
ADCY1	adenylate cyclase 1	receptor-signaling	Reactome: R-HSA-170	Drucker 2018, PMID: 29	232	Yes
ADCY2	adenylate cyclase 2	receptor-signaling	Reactome: R-HSA-163	Drucker 2018, PMID: 29	233	Yes
ADCY3	adenylate cyclase 3	receptor-signaling	Reactome: R-HSA-418	Drucker 2018, PMID: 29	234	Yes
ADCY5	adenylate cyclase 5	receptor-signaling	Reactome: R-HSA-164	Drucker 2018, PMID: 29	236	Yes
ADCY6	adenylate cyclase 6	receptor-signaling	Reactome: R-HSA-381	Drucker 2018, PMID: 29	237	Yes
CREB1	cAMP responsive element	receptor-signaling	Reactome: R-HSA-111	Drucker 2018, PMID: 29	2345	Yes
GLP1R	glucagon like peptide 1 re	receptor-signaling	Reactome: R-HSA-381	Drucker 2018, PMID: 29	4324	Yes
GNAS	GNAS complex locus	receptor-signaling	Reactome: R-HSA-381	Drucker 2018, PMID: 29	4392	Yes
PDE3B	phosphodiesterase 3B	receptor-signaling	Reactome: R-HSA-970	Drucker 2018, PMID: 29	8779	Yes
PDE4B	phosphodiesterase 4B	receptor-signaling	Reactome: R-HSA-964	Drucker 2018, PMID: 29	8781	Yes
PRKACA	protein kinase cAMP-activ	receptor-signaling	Reactome: R-HSA-163	Drucker 2018, PMID: 29	9380	Yes
PRKACB	protein kinase cAMP-activ	receptor-signaling	Reactome: R-HSA-163	Drucker 2018, PMID: 29	9381	Yes
PRKACG	protein kinase cAMP-activ	receptor-signaling	Reactome: R-HSA-163	Drucker 2018, PMID: 29	9382	Yes
PRKAR1A	protein kinase cAMP-depe	receptor-signaling	Reactome: R-HSA-163	Drucker 2018, PMID: 29	9388	Yes
PRKAR1B	protein kinase cAMP-depe	receptor-signaling	Reactome: R-HSA-163	Drucker 2018, PMID: 29	9390	Yes
PRKAR2A	protein kinase cAMP-depe	receptor-signaling	Reactome: R-HSA-163	Drucker 2018, PMID: 29	9391	Yes
PRKAR2B	protein kinase cAMP-depe	receptor-signaling	Reactome: R-HSA-163	Drucker 2018, PMID: 29	9392	Yes
RAPGEF3	Rap guanine nucleotide ex	receptor-signaling	Reactome: R-HSA-381	Drucker 2018, PMID: 29	16629	Yes
RAPGEF4	Rap guanine nucleotide ex	receptor-signaling	Reactome: R-HSA-381	Drucker 2018, PMID: 29	16626	Yes

Table S2:

Item	Key setting	Specific values / file name(s)	Reproducibility notes
PDB preprocessing (exact steps)	Structure source & selection	PDB 9GYO, 7CFN, 7XTQ, 7BW0 (human TGR5–Gs complexes)	Downloaded uniformly on the data-freeze date; retained only the receptor chain and co-crystallized ligand; removed G-protein chains, ions, detergents/surfactants, and waters (retaining only ligand-neighboring crystallographic waters if involved in coordination); disulfide bonds were preserved.
	Missing residues & protonation	MODELLER used to repair short missing loops and missing side chains; PROPKA at pH 7.4 used to assign protonation states; His assigned as HID/HIE based on H-bond geometry and microenvironment; termini charged according to pH 7.4	After processing, pdbfix was used for standard checks of connectivity and atom types; all coordinates were kept in the receptor's reference frame without global rebuilding.
	Pocket & docking grid	Docking grid centered at the centroid of the co-crystallized ligand; box edge length 20.5–24.0 Å, optimized with 0.5 Å increments	For Vina/GNINA, conf files specify center_x/y/z and size_x/y/z, and final selected values were recorded; the grid selection procedure is documented in Supplementary S2.
Number of ligand states after tautomer/ionization filtering	State generation & filtering	Open Babel at pH 7.4 to generate tautomers/ionization states; RDKit for deduplication; filtered by predicted relative energy and dominant population	Only the most stable microstate was retained for each compound (n = 1); recorded charge and dominant state: INT-777 (−1, bile-acid carboxylate); tetrahydrocurcumin (0, neutral); curcumin (0, neutral); demethoxycurcumin (0, neutral); bisdemethoxycurcumin (0, neutral); curcumin-glucuronide (−1, carboxylate); curcumin-sulfate (−1, sulfate ester).
Random seeds for MD replicates (3 replicates/system)	Velocity generation gen_seed (310 K, NVT start)	INT-777: 712943, 184267, 953128; tetrahydrocurcumin: 628317, 470293, 915642; curcumin: 532861, 207439, 861274; demethoxycurcumin: 419872, 736291, 594386; bisdemethoxycurcumin: 803417, 265938, 947123; curcumin-glucuronide: 358219, 621487, 790436; curcumin-sulfate: 274593, 918362, 546981	In .mdp: gen_vel = yes, gen_temp = 310, gen_seed set as above; the three replicates used identical topology/constraints but different gen_seed values; all other parameters were consistent with Section 2.5.
Snapshot extraction for MM-PBSA	Sampling window & interval	Post-equilibration production 100–200 ns; 50 evenly spaced frames per replicate	For each replicate, gmx trjconv extracted frames from t = 100.00 ns to 200.00 ns with a 2.00 ns interval (50 frames total); each replicate was computed independently and combined as mean with BCa 95% CI; index file includes complex/receptor/ligand groups.

Table S3:

Scenario ID	w_dock	w_MD	w_net	w_ADMET	Direct-path	Rank vs inc	DeltaRank	Spearman rho
Baseline	0.30	0.25	0.25	0.20	0.68	Direct pref	+0	1.00
dock+20%,	0.32	0.27	0.27	0.14	0.73	Direct pref	+0	0.96
dock+20%,	0.33	0.27	0.18	0.22	0.67	Direct pref	+0	0.96
dock+20%,	0.35	0.29	0.20	0.16	0.72	Direct pref	+0	0.95
dock+20%,	0.33	0.18	0.27	0.22	0.67	Direct pref	+0	0.96
dock+20%,	0.35	0.20	0.29	0.16	0.72	Direct pref	+0	0.95
dock+20%,	0.36	0.20	0.20	0.24	0.66	Direct pref	+0	0.94
dock+20%,	0.39	0.22	0.22	0.17	0.72	Direct pref	+0	0.95
dock−20%,	0.22	0.28	0.28	0.22	0.65	Tie	+0	0.95
dock−20%,	0.24	0.30	0.30	0.16	0.70	Direct pref	+0	0.94
dock−20%,	0.24	0.31	0.20	0.24	0.64	Tie	+0	0.94
dock−20%,	0.27	0.33	0.22	0.18	0.69	Direct pref	+0	0.95
dock−20%,	0.24	0.20	0.31	0.24	0.64	Tie	+0	0.94
dock−20%,	0.27	0.22	0.33	0.18	0.69	Direct pref	+0	0.95
dock−20%,	0.27	0.23	0.23	0.27	0.62	Tie	+1	0.96
Leave-one-	0.00	0.36	0.36	0.29	0.57	Indirect pr	+2	0.82
Leave-one-	0.40	0.00	0.33	0.27	0.64	Tie	+1	0.85
Leave-one-	0.40	0.33	0.00	0.27	0.64	Tie	+1	0.85
Leave-one-	0.37	0.31	0.31	0.00	0.85	Direct pref	−2	0.88