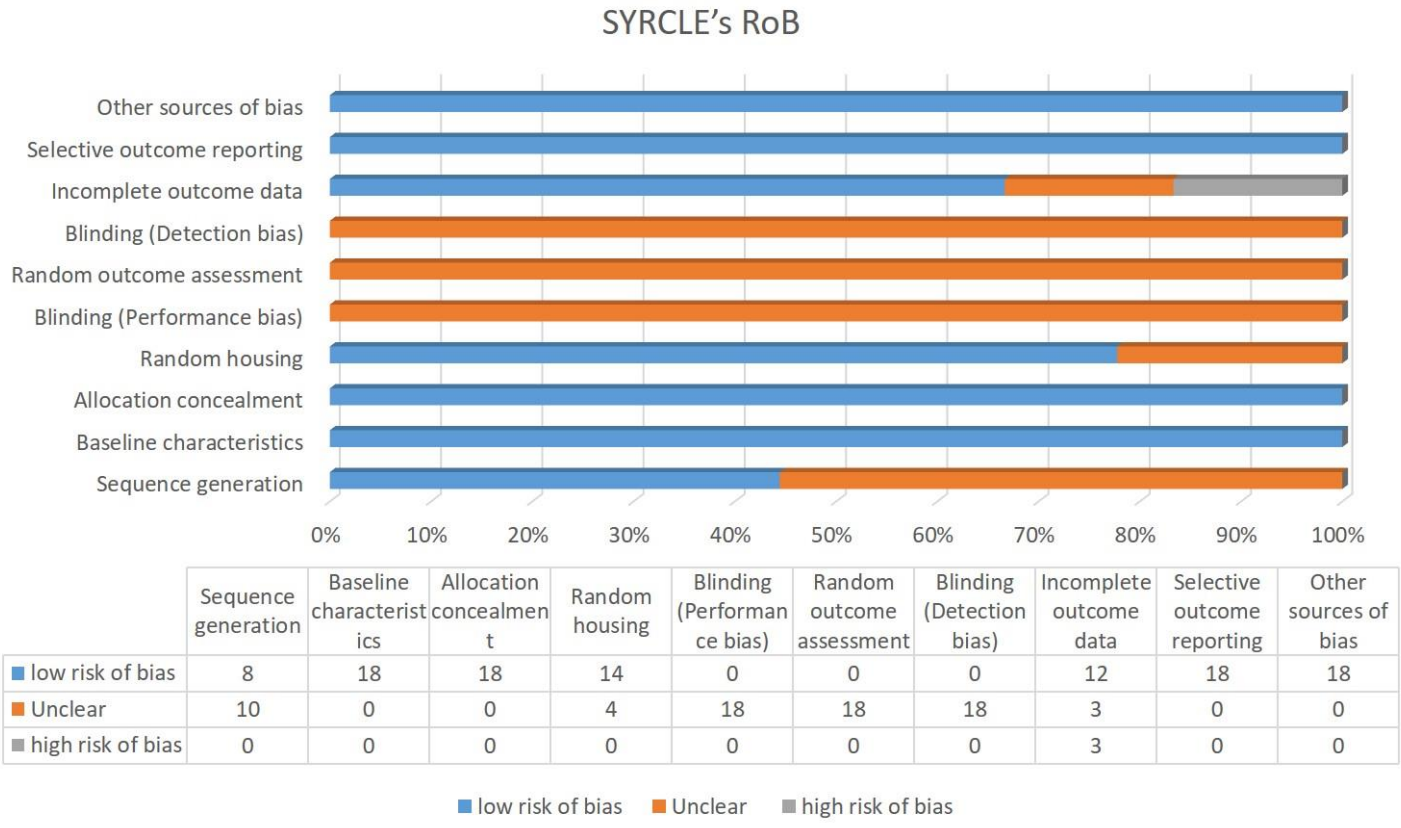
PubMed: ("isoliquiritigenin"[All Fields] OR "2',4',4-trihydroxychalcone "[All Fields] OR "6'-deoxychalcone"[All Fields] OR " GU 17"[All Fields] OR " GU-17"[All Fields] OR "Isoliquiritigenin phosphate ammonium salt"[All Fields] OR " isoliquiritigenin 2'-methyl ether "[All Fields] OR ("isoliquiritigenin 2'-methyl ether "[Supplementary Concept] OR "isoliquiritigenin 2 methyl ether"[All Fields])) AND ("breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]) = 43

Scopus: TITLE-ABS-KEY ((isoliquiritigenin OR “2',4',4-trihydroxychalcone” OR “6'-deoxychalcone” OR “GU 17” OR “GU-17” OR “Isoliquiritigenin phosphate ammonium salt” OR “isoliquiritigenin 2'-methyl ether” OR “ILME ether cpd”) AND ("breast neoplasm" OR “breast neoplasms” OR "breast cancer" OR "breast cancers")) = 3,675

Embase: (isoliquiritigenin OR “2',4',4-trihydroxychalcone” OR “6'-deoxychalcone” OR “GU-17” OR “Isoliquiritigenin phosphate ammonium salt” OR “isoliquiritigenin 2'-methyl ether” OR “ILME ether cpd”) AND ("breast neoplasm" OR “breast neoplasms” OR "breast cancer" OR "breast cancers") = 573

Appendix 1. Search strategy used to identify relevant studies reporting the effect of ISL on breast cancer prevention and the modulation of metastatic processes using international scientific databases (PubMed, Scopus and Embase). Numbers of studies are indicated behind the database names.



	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding (Performance bias)	Random outcome assessment	Blinding (Detection bias)	Incomplete outcome data	Selective outcome reporting	Other sources of bias
low risk of bias	8	18	18	14	0	0	0	12	18	18
Unclear	10	0	0	4	18	18	18	3	0	0
high risk of bias	0	0	0	0	0	0	0	3	0	0

Appendix 2. SYRCLE's Risk-of-Bias Assessment Across Ten Methodological Domains in 18 Preclinical Breast Cancer Studies.

Appendix 3.. Summary of Risk of Bias Evaluation for in Vivo Studies Using SYRCLE's RoB Instrument

author	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding (Performance bias)	Random outcome assessment	Blinding (Detection bias)	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Ganesan et al. 2024[1]	√	√	√	√	Uc	Uc	uc	√	√	√
Ganesan et al. 2024[2]	Uc	√	√	Uc	Uc	Uc	Uc	uc	√	√
gao et al. 2017[3]	Uc	√	√	√	Uc	Uc	uc	X	√	√
Li et al. 2013[4]	√	√	√	√	Uc	Uc	uc	√	√	√
Lin et al. 2020[5]	√	√	√	√	Uc	Uc	uc	√	√	√
Peng et al. 2020[6]	Uc	√	√	√	Uc	Uc	uc	√	√	√
Sun et al. 2023[7]	Uc	√	√	√	Uc	Uc	uc	uc	√	√
Wang et al. 2013[8]	Uc	√	√	Uc	Uc	Uc	uc	√	√	√
wang et al. 2014[9]	Uc	√	√	Uc	Uc	Uc	uc	X	√	√
Wang et al. 2014[10]	Uc	√	√	Uc	Uc	Uc	uc	uc	√	√
Wang et al. 2015[11]	Uc	√	√	√	Uc	Uc	uc	√	√	√
Wang et al. 2023[12]	√	√	√	√	Uc	Uc	uc	√	√	√
Xie et al. 2025[13]	Uc	√	√	√	Uc	Uc	uc	X	√	√
Xu et al. 2025[14]	√	√	√	√	Uc	Uc	uc	√	√	√
Yuan et al. 2024[15]	√	√	√	√	Uc	Uc	uc	√	√	√

zheng et al. 2014[16]	√	√	√	√	Uc	Uc	uc	√	√	√
Peng et al. 2021[17]	√	√	√	√	Uc	Uc	uc	√	√	√
Tang et al. 2018[18]	Uc	√	√	√	Uc	Uc	uc	√	√	√

√, low risk of bias; X, high risk of bias; Un, Unclear

Appendix 4. Summary of Quality Appraisal for in Vitro Studies Based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Instrument

author	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Magnitude of Moderate/Significant Effect**	**Effect of Dose**	**Overall Quality**
Crone et al. 2019[19]	X: Insufficient data were reported for certain outcomes.	√	√	√	√	√	√	moderate
Das et al. 2023[20]	√	√	√	√	√	√	√	high
Dunlap et al. 2015[21]	√	√	√	√	√	√	√	high
Ganesan et al. 2024[1]	√	√	√	√	√	√	√	high
Ganesan et al. 2024[22]	√	√	√	√	√	√	√	high
gao et al. 2017[23]	√	√	√	√	√	√	√	high
Hsia et al. 2012[24]	√	√	√	√	√	√	√	high
lau et al. 2009[25]	X: Insufficient data were reported for certain outcomes.	√	√	√	√	√	√	moderate
Lee et al. 2015[26]	X: Insufficient data were	√	√	√	√	√	√	moderate

	reported for certain outcomes.							
Li et al. 2013[27]	√	√	√	√	√	√	√	high
Li et al. 2022[28]	X: Insufficient data were reported for certain outcomes.	√	√	√	√	√	√	moderate
Lin et al. 2020[29]	√	√	√	√	√	√	√	high
maggiolini et al. 2002[30]	√	√	√	√	√	√	√	high
Ning et al. 2016[31]	X: Insufficient data were reported for certain outcomes.	√	√	√	√	√	√	moderate
Ning et al. 2017[32]	√	√	√	√	√	√	√	high
peng et al. 2016[33]	X: Insufficient data were reported for certain outcomes.	√	√	√	√	√	√	moderate
Peng et al. 2017[34]	√	√	√	√	√	√	√	high
Peng et al. 2020[35]	√	√	√	√	√	√	√	high
Peng et al. 2021[36]	√	√	√	√	√	√	√	high
Sun et al. 2023[37]	√	√	√	√	√	√	√	high
Tang et al. 2018[18]	X: Insufficient data were reported for certain outcomes.	√	√	√	√	√	√	moderate
Wang et al. 2013[38]	√	√	√	√	√	√	√	high

wang et al. 2013[39]	√	√	√	√	√	√	√	high
wang et al. 2014[9]	√	√	√	√	√	√	√	high
Wang et al. 2014[40]	√	√	√	√	√	√	√	high
Wang et al. 2015[41]	√	√	√	√	√	√	√	high
Wang et al. 2023[12]	√	√	√	√	√	√	√	high
Wong et al. 2014[42]	√	√	√	√	√	√	√	high
Xie et al. 2025[13]	√	√	√	√	√	√	√	high
Xu et al. 2025[14]	√	√	√	√	√	√	√	high
ye et al. 2009[43]	√	√	√	√	√	√	√	high
Yuan et al. 2024[15]	√	√	√	√	√	√	√	high
zheng et al. 2014[16]	√	√	√	√	√	√	√	high

Appendix 5. Overview of Quality Appraisal for in Vivo Studies Based on the ARRIVE Essential 10 Criteria

author	1	2	3	4	5	6	7	8	9	10	Quality
Ganesan et al. 2024[1]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
Ganesan et al. 2024[2]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
gao et al. 2017[3]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
Li et al. 2013[4]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
Lin et al. 2020[5]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
Peng et al. 2020[6]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
Sun et al. 2023[7]	√	Uc/NE	Uc/NE	√	Uc/NE	√	√	√	√	√	High
Wang et al. 2013[8]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
wang et al. 2014[9]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High

Wang et al. 2014[10]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
Wang et al. 2015[11]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
Wang et al. 2023[12]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
Xie et al. 2025[13]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
Xu et al. 2025[14]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
Yuan et al. 2024[15]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
zheng et al. 2014[16]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
Peng et al. 2021[17]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High
Tang et al. 2018[18]	√	√	Uc/NE	Uc/NE	Uc/NE	√	√	√	√	√	High

√, yes; X, no; Un/NE, Unclear/ Not Evaluated

The ARRIVE Essential 10 checklist items: 1, Study Design; 2, Sample Size; 3, Inclusion and Exclusion Criteria; 4, Randomisation; 5, Blinding; 6, Outcome Measures; 7, Statistical Methods; 8, Experimental Animals; 9, Experimental Procedures; 10, Results.

1. Ganesan K, Xu C, Xie C, et al. Cryoprotective isoliquiritigenin-zein phosphatidylcholine nanoparticles inhibits breast cancer-bone metastasis by targeting JAK-STAT signaling pathways. *Chem Biol Interact*. Jun 1 2024;396:111037. doi:10.1016/j.cbi.2024.111037
2. Ganesan K, Gao F, Zheng C, et al. Isoliquiritigenin-infused electrospun nanofiber inhibits breast cancer proliferation and invasion through downregulation of PI3K/Akt/mTOR and MMP2/9 pathways. Article. *Journal of Drug Delivery Science and Technology*. 2024;96105609. doi:10.1016/j.jddst.2024.105609
3. Gao F, Zhang J, Fu C, et al. iRGD-modified lipid–polymer hybrid nanoparticles loaded with isoliquiritigenin to enhance anti-breast cancer effect and tumor-targeting ability. *International journal of nanomedicine*. 2017:4147-4162.
4. Li Y, Zhao H, Wang Y, et al. Isoliquiritigenin induces growth inhibition and apoptosis through downregulating arachidonic acid metabolic network and the deactivation of PI3K/Akt in human breast cancer. *Toxicol Appl Pharmacol*. Oct 1 2013;272(1):37-48. doi:10.1016/j.taap.2013.05.031
5. Lin PH, Chiang YF, Shieh TM, et al. Dietary Compound Isoliquiritigenin, an Antioxidant from Licorice, Suppresses Triple-Negative Breast Tumor Growth via Apoptotic Death Program Activation in Cell and Xenograft Animal Models. *Antioxidants (Basel)*. Mar 10 2020;9(3)doi:10.3390/antiox9030228
6. Peng F, Xiong L, Xie X, Tang H, Huang R, Peng C. Isoliquiritigenin Derivative Regulates miR-374a/BAX Axis to Suppress Triple-Negative Breast Cancer Tumorigenesis and Development. Article. *Frontiers in Pharmacology*. 2020;11378. doi:10.3389/fphar.2020.00378
7. Sun F, Shen H, Liu Q, et al. Powerful synergy of traditional Chinese medicine and aggregation-induced emission-active photosensitizer in photodynamic therapy. *ACS nano*. 2023;17(19):18952-18964.
8. Wang Z, Wang N, Han S, et al. Dietary Compound Isoliquiritigenin Inhibits Breast Cancer Neoangiogenesis via VEGF/VEGFR-2 Signaling Pathway. Article. *PLoS ONE*. 2013;8(7)e68566. doi:10.1371/journal.pone.0068566
9. Wang N, Wang Z, Peng C, et al. Dietary compound isoliquiritigenin targets GRP78 to chemosensitize breast cancer stem cells via β-catenin/ABCG2 signaling. Article. *Carcinogenesis*. 2014;35(11):2544-2554. doi:10.1093/carcin/bgu187
10. Wang Z, Wang N, Liu P, et al. MicroRNA-25 regulates chemoresistance-associated autophagy in breast cancer cells, a process modulated by the natural autophagy inducer isoliquiritigenin. Article. *Oncotarget*. 2014;5(16):7013-7026. doi:10.18632/oncotarget.2192

11. Wang N, Wang Z, Wang Y, et al. Dietary compound isoliquiritigenin prevents mammary carcinogenesis by inhibiting breast cancer stem cells through WIF1 demethylation. *Oncotarget*. 2015;6(12):9854-76. doi:10.18632/oncotarget.3396
12. Wang Y, Zhang C, Xiao M, et al. A tumor-targeted delivery of oral isoliquiritigenin through encapsulated zein phosphatidylcholine hybrid nanoparticles prevents triple-negative breast cancer. Article. *Journal of Drug Delivery Science and Technology*. 2023;79103922. doi:10.1016/j.jddst.2022.103922
13. Xie Y, Xie J, Huang G, et al. Isoliquiritigenin reduces brain metastasis by circNAV3-ST6GALNAC5-EGFR axis in triple-negative breast cancer. Article. *Cancer Letters*. 2025;624217734. doi:10.1016/j.canlet.2025.217734
14. Xu C, Zhang C, Ganesan K, et al. Anti-migratory Properties of Cryoprotective Isoliquiritigenin-zein Phosphatidylcholine Nanoparticles Prevent Triple-negative Breast Cancer through PI3K-mTOR and MMP2/9 Pathways. *Curr Med Chem*. 2025;32(9):1770-1788. doi:10.2174/0109298673259973231023110945
15. Yuan CL, Yang XL, Sun L, Jiang YX, Zhang DD, Huang S. Isoliquiritigenin Suppresses Breast Tumor Development by Enhancing Host Antitumor Immunity. *Am J Chin Med*. 2024;52(6):1819-1841. doi:10.1142/s0192415x2450071x
16. Zheng H, Li Y, Wang Y, et al. Downregulation of COX-2 and CYP 4A signaling by isoliquiritigenin inhibits human breast cancer metastasis through preventing anoikis resistance, migration and invasion. Article. *Toxicology and Applied Pharmacology*. 2014;280(1):10-20. doi:10.1016/j.taap.2014.07.018
17. Peng F, Tang H, Du J, Chen J, Peng C. Isoliquiritigenin Suppresses EMT-Induced Metastasis in Triple-Negative Breast Cancer through miR-200c/C-JUN/β-Catenin. *Am J Chin Med*. 2021;49(2):505-523. doi:10.1142/s0192415x21500233
18. Tang H, Peng F, Huang X, et al. Neoisoliquiritigenin inhibits tumor progression by targeting GRP78-β-catenin signaling in breast cancer. *Current cancer drug targets*. 2018;18(4):390-399.
19. Crone M, Lloyd V, Szmyd M, et al. MON-038 The Effects of Isoliquiritigenin (ISL) on the Expression of Estrogen Receptor and Tumor Suppressor Genes BRCA-1 and P53 in Breast Cancer Cells. *Journal of the Endocrine Society*. 2019;3(Supplement_1):MON-038.
20. Das A, Prajapati A, Karna A, et al. Structure-based virtual screening of chemical libraries as potential MELK inhibitors and their therapeutic evaluation against breast cancer. *Chem Biol Interact*. May 1 2023;376:110443. doi:10.1016/j.cbi.2023.110443
21. Dunlap TL, Wang S, Simmler C, et al. Differential Effects of Glycyrrhiza Species on Genotoxic Estrogen Metabolism: Licochalcone A Downregulates P450 1B1, whereas Isoliquiritigenin Stimulates It. *Chem Res Toxicol*. Aug 17 2015;28(8):1584-94. doi:10.1021/acs.chemrestox.5b00157
22. Ganesan K, Gao F, Zheng C, et al. Isoliquiritigenin-infused electrospun nanofiber inhibits breast cancer proliferation and invasion through downregulation of PI3K/Akt/mTOR and MMP2/9 pathways. *Journal of Drug Delivery Science and Technology*. 2024;96:105609.
23. Gao F, Zhang J, Fu C, et al. iRGD-modified lipid–polymer hybrid nanoparticles loaded with isoliquiritigenin to enhance anti-breast cancer effect and tumor-targeting ability. Article. *International Journal of Nanomedicine*. 2017;12:4147-4162. doi:10.2147/IJN.S134148
24. Hsia S-M, Shieh T-M, Shih Y-H. Effects of isoliquiritigenin (ISL) on VEGF secretion in Human breast cancer cell line MDA-MB-231. *Cancer Research*. 2012;72(8_Supplement):1991-1991.
25. Lau GT, Ye L, Leung LK. The licorice flavonoid isoliquiritigenin suppresses phorbol ester-induced cyclooxygenase-2 expression in the non-tumorigenic MCF-10A breast cell line. *Planta Med*. May 2010;76(8):780-5. doi:10.1055/s-0029-1240699
26. Lee SK, Park K-K, Kim KR, Kim H-J, Chung W-Y. Isoliquiritigenin inhibits metastatic breast cancer cell-induced receptor activator of nuclear factor kappa-B ligand/osteoprotegerin ratio in human osteoblastic cells. *Journal of Cancer Prevention*. 2015;20(4):281.
27. Li Y, Zhao H, Wang Y, et al. Isoliquiritigenin induces growth inhibition and apoptosis through downregulating arachidonic acid metabolic network and the deactivation of PI3K/Akt in human breast cancer. *Toxicology and applied pharmacology*. 2013;272(1):37-48.
28. Li M, Lu G, Ma X, et al. Anti-inflammation of isoliquiritigenin via the inhibition of NF-κB and MAPK in LPS-stimulated MAC-T cells. *BMC Veterinary Research*. 2022;18(1):320.
29. Lin P-H, Chiang Y-F, Shieh T-M, et al. Dietary compound isoliquiritigenin, an antioxidant from licorice, suppresses triple-negative breast tumor growth via apoptotic death program activation in cell and xenograft animal models. *Antioxidants*. 2020;9(3):228.

30. Maggiolini M, Statti G, Vivacqua A, et al. Estrogenic and antiproliferative activities of isoliquiritigenin in MCF7 breast cancer cells. *J Steroid Biochem Mol Biol*. Nov 2002;82(4-5):315-22. doi:10.1016/s0960-0760(02)00230-3
31. Ning S, Mu J, Shen Z, et al. Isoliquiritigenin attenuates the invasive capacity of breast cancer cells via up-regulating the tumor suppressor RECK. Article. *RSC Advances*. 2016;6(29):24719-24727. doi:10.1039/c5ra26759e
32. Ning S, Ma X, Zhu D, et al. Isoliquiritigenin attenuates MiR-21 expression via induction of PIAS3 in breast cancer cells. Article. *RSC Advances*. 2017;7(29):18085-18092. doi:10.1039/c6ra25511f
33. Peng F, Meng C-W, Zhou Q-M, Chen J-P, Xiong L. Cytotoxic evaluation against breast cancer cells of isoliquiritigenin analogues from Spatholobus suberectus and their synthetic derivatives. *Journal of natural products*. 2016;79(1):248-251.
34. Peng F, Tang H, Liu P, et al. Isoliquiritigenin modulates miR-374a/PTEN/Akt axis to suppress breast cancer tumorigenesis and metastasis. *Scientific reports*. 2017;7(1):9022.
35. Peng F, Xiong L, Xie X, Tang H, Huang R, Peng C. Isoliquiritigenin derivative regulates miR-374a/BAX axis to suppress triple-negative breast cancer tumorigenesis and development. *Frontiers in Pharmacology*. 2020;11:378.
36. Peng F, Tang H, Du J, Chen J, Peng C. Isoliquiritigenin suppresses EMT-induced metastasis in triple-negative breast cancer through miR-200c/c-Jun/β-Catenin. *The American journal of Chinese medicine*. 2021;49(02):505-523.
37. Sun F, Shen H, Liu Q, et al. Powerful Synergy of Traditional Chinese Medicine and Aggregation-Induced Emission-Active Photosensitizer in Photodynamic Therapy. Article. *ACS Nano*. 2023;17(19):18952-18964. doi:10.1021/acsnano.3c04342
38. Wang Z, Wang N, Han S, et al. Dietary compound isoliquiritigenin inhibits breast cancer neoangiogenesis via VEGF/VEGFR-2 signaling pathway. *PloS one*. 2013;8(7):e68566.
39. Wang KL, Hsia SM, Chan CJ, et al. Inhibitory effects of isoliquiritigenin on the migration and invasion of human breast cancer cells. Article. *Expert Opinion on Therapeutic Targets*. 2013;17(4):337-349. doi:10.1517/14728222.2013.756869
40. Wang Z, Wang N, Liu P, et al. MicroRNA-25 regulates chemoresistance-associated autophagy in breast cancer cells, a process modulated by the natural autophagy inducer isoliquiritigenin. *Oncotarget*. 2014;5(16):7013.
41. Wang N, Wang Z, Wang Y, et al. Dietary compound isoliquiritigenin prevents mammary carcinogenesis by inhibiting breast cancer stem cells through WIF1 demethylation. Article. *Oncotarget*. 2015;6(12):9854-9876. doi:10.18632/oncotarget.3396
42. Wong TY, Lin SM, Poon CH, Leung LK. The licorice flavonoid isoliquiritigenin reduces DNA-binding activity of AhR in MCF-7 cells. Article. *Chemico-Biological Interactions*. 2014;221:70-76. doi:10.1016/j.cbi.2014.07.015
43. Ye L, Gho WM, Chan FL, Chen S, Leung LK. Dietary administration of the licorice flavonoid isoliquiritigenin deters the growth of MCF-7 cells overexpressing aromatase. *Int J Cancer*. Mar 1 2009;124(5):1028-36. doi:10.1002/ijc.24046