# Isoliquiritigenin in Cancer

Subjects: Oncology

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Isoliquiritigenin (ISL), a natural bioactive compound with a chalcone structure, demonstrates high antitumor efficacy.

isoliquiritigenin cancer

## 1. Indroduction

ISL is a flavonoid with a simple chalcone structure. The structure of ISL and its metabolites are shown in Figure 1. The previous studies demonstrated the six metabolites detected in phase I[1][2][3], including liquritigenin (M1), 2′,4,4′,5′-tetrahydroxychalcone (M2), sulfuretin (M3), butein (M4), davidigenin (M5), and *cis*-6,4′-dihydroxyaurone (M6). Among the six metabolites, butein is the more active metabolite in the liver and in HT22 cells, with significant distribution on M1, M3, and M4 (Figure 1) [1][2][4]. Moreover, the previous study reported that the dominant metabolites of ISL are THC (2,4,2′,4′-tetrahydroxychalcone) and naringenin chalcone in lung cells [5] In vivo absorption of ISL occurs in the intestines, transported to the liver for phase II biotransformation[2]. In phase II metabolism, liquiritigenin, glucuronidated ISL, glucuronidated liquiritigenin, and glucuronidated ISL are produced. Only glucuronidated liquiritigenin is predominant[6]. Many studies have suggested that secondary metabolites are involved in different biological activities and pharmaceuticals[1][2][6][7]. Therefore, these metabolites may differ in various cell lines or organs; however, they all share a similar structure to that of chalcone, which contains two aromatic rings connected by an unsaturated carbon chain, resulting in interconnected biological activities.

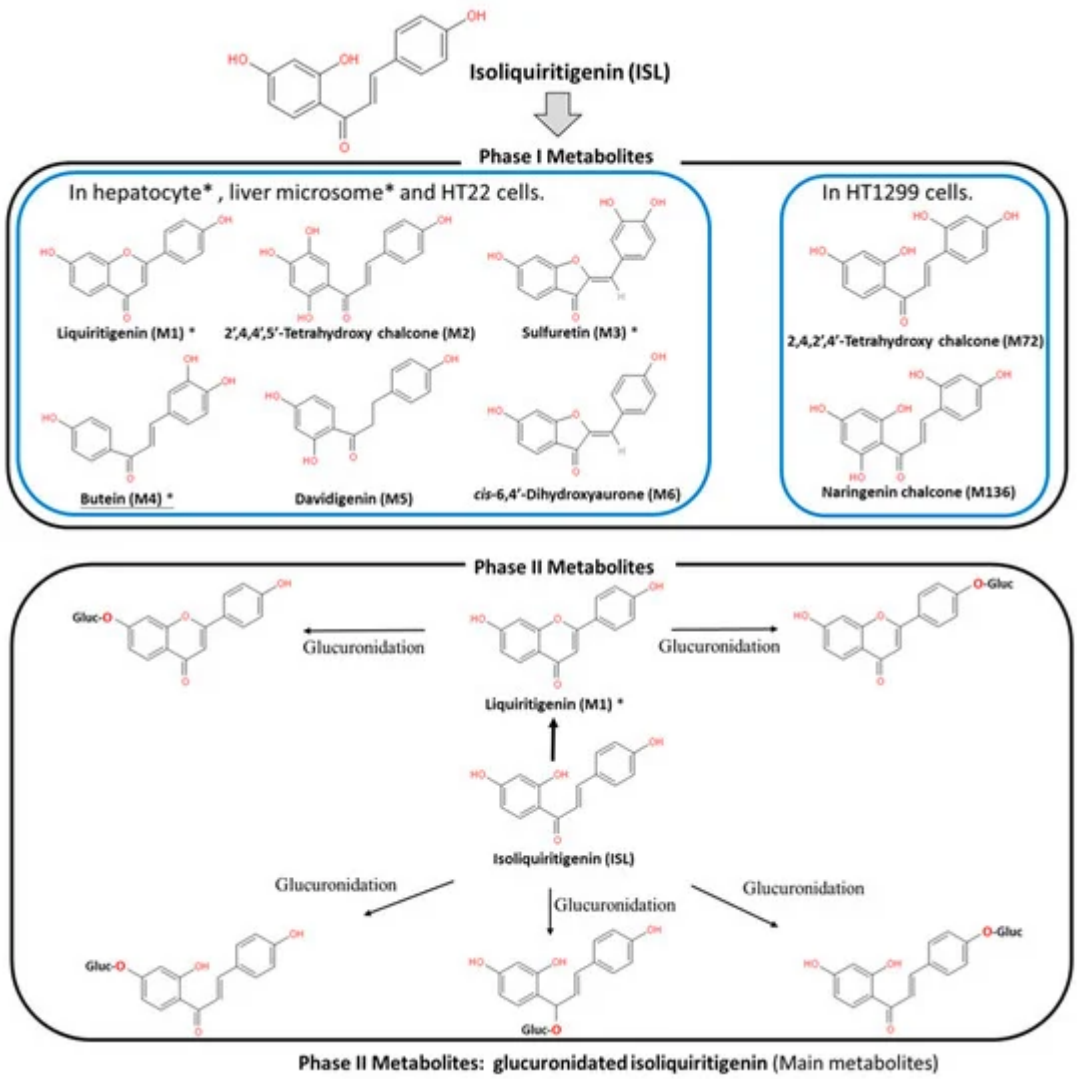


**Figure 1.** Metabolites of isoliquiritigenin (ISL). Phase I ISL metabolites were identified to be liquiritigenin (M1), 2′,4,4′,5′-tetrahydroxychalcone (M2), sulfuretin (M3), butein (M4), davidigenin (M5), and *cis*-6,4′-dihydroxyaurone (M6). Phase II metabolites were glucuronide conjugated process. Note: Figure was modified from[1][2].

## 2. ISL Pharmacokinetics

Evaluation of the safety of ISL is necessary for future clinical applications. Therefore, many studies, through different routes of administrations, including intravenously (IV), via hypodermic (IH) or intraperitoneal (IP) injection, and orally, have indicated that ISL exhibits a robust absorption capacity (absorption rate: ~60–90 min; oral absorption: >90%) with a strong elimination ability ($t_{1/2}$: 2–4.9 h)[6][8][9][10]. Moreover, the data showed similar trends among different analytic methods, including high-performance liquid chromatography (HPLC), HPLC–MS/MS, and fluorescence spectrometry (SFS)[6][8][9]. This means that the absorption of ISL is quickly and widely distributed throughout the body[6][8][9][10]. Concentrations of ISL may vary in different tissues, including the heart, liver, lungs, spleen, kidneys, brain, muscles, and fat. ISL distribution mainly relies on the blood circulation, with the brain showing the lowest level of ISL due to the blood–brain barrier (BBB). These results imply that ISL is able to penetrate the BBB and exhibits neuroprotective activity in a male middle cerebral artery occlusion (MCAO)-induced

focal cerebral ischemia rat model and high fat diet (HFD)-induced ICR mice model[11][12]. Interestingly, only after oral administration does $[ISL]_{plasma}$ exhibit a double-peak of ISL[10][13][14][15], the possible mechanism for which has been proposed as enterohepatic recycling. As a matter of fact, oral administration has become the most advanced application route.

## 3. ISL Nanoformulations and ISL Derivatives: Improved Efficacy

Generally speaking, poor bioavailability, rapid degradation, fast metabolism, and systemic elimination are the essential factors that lead to insufficient bioavailability. Insufficient bioavailability of ISL means that its efficacy is far less than 20%[6] [10]. The term insufficient bioavailability implies that patients show intolerance to bulk administration of ISL to reach the desired effect, thereby highlighting the need to improve its effectiveness. To improve solubility, enhancing its bioavailability and distribution, encapsulated ISL nanoparticles or nano-ISL have been developed. Below, we summarize various ISL nanoparticles applied in preclinical studies, for example, polymer nanoparticles, liposomes, micelles, solid lipid nanoparticles (SLNs), and polymer conjugates.

- Nanosuspension: ISL is milled with HPC (hydroxypropyl cellulose) SSL and PVP (polyvinylpyrrolidone) K30 to form a lamelliform or ellipse shape of the nanosuspension. HPC SSL and PVP K30 act as stabilizer. These two nanosuspension particles (size: 238.1 ± 4.9 nm with SSL; 354.1 ± 9.1 nm with K30) do not only improve the solubility issue, but also enhance the cytotoxicity a 7.5–10-fold[16].

- Nanoencapsulation: Mesoporous silica nanoparticles (MSNs) are a solid material, acting as a biodegradable nanoscale drug carrier. When MSNs are encapsulated with ISL, they improve the efficacy of ISL in vitro and in vivo[17].

- Lipid–polymer hybrid nanoparticle system:

  3.1. iRGD hybrid NPs: The composition of lipid–polymer hybrid nanoparticles (NPs) include lactic-co-glycolic acid (PLGA), lecithin, and a hydrophilic poly-ethylene-glycol (PEG). ISL-loaded hybrid NPs are composed of an inner PLGA core with an outer lipid layer (PEG, lecithin, and iRGD peptides). iRGD peptides (CRGDK/RGPD/EC, a tumor-homing peptides), can deliver drugs to a tumor. In vitro, ISL–iRGD NPs show stronger inhibition effects and induce apoptosis effects. In vivo, ISL–iRGD NPs show stronger effects in the viability of tumor cells. Herein, iRGD-modified lipid–polymer NPs showed better solubility, bioavailability, and targeting distribution[18].

  3.2. Hydrophilic polyanion solid lipid nanoparticles (SLNs): SLNs are composed of natural lipids such as lecithin or triglycerides that remain solid at 37 °C. SLNs can protect labile compounds from chemical degradation and can improve bioavailability. Low-molecular-weight heparins (LMWHs) are fragments of heparin showing hydrophilic polyanions that can improve the efficacy of ISL[19].

- Microemulsion: The self-microemulsifying drug delivery system (SEMDDS) was designed for improving the solubility, absorption, and bioavailability of lipophilic drugs. The SMEDDS comprises ethyl oleate (EO; oil phase), Tween 80 (surfactant), and PEG 400 (co-surfactant). ISL-loaded SMEDDS has been proven to improve the solubility and oral in vivo availability[13].

- ISL-loaded nanostructured lipid carriers (ISL-NLCs): NLCs mix solid lipids with spatially incompatible liquid lipids, which leads to a special nanostructure with improved properties for drug loading. ISL-loaded NLCs are constructed by glycerol monostearate (MS) and Mi-glyol-812 as the solid and liquid lipid materials to carry the ISL[20]. In pharmacokinetic studies, less than 10% of the NLCs remains in the stomach after oral administration, mainly absorbed in the colon[19]. Moreover, the antitumor effect of ISL-loaded NLCs has been evaluated in sarcoma 180 (S180)-bearing and murine hepatoma (H22)-bearing mice models via IP administration[20]. A biodistribution study showed that the ISL concentration of ISL-loaded NLCs in the tumor is higher 2.5-fold than free ISL. In a skin permeability study, the previous study suggested NLCs as a promising carrier to deliver the ISL[21].

- TPGS-modified proliposomes: D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) has been selected as an excipient for ISL-loaded TPGS-modified proliposomes (ISL-TPGS-PLP), prepared using the film dispersion method with ISL-loaded proliposomes (ISL–PLP). ISL-TPGS-PLP can enhance the solubility, bioavailability and liver-targeting ability of ISL[14].

- Polymeric micelles: PEO (polyethylene oxide)–PPO (polypropylene oxide)–PEO (polyethylene oxide) triblock copolymers are highly biocompatible and act as surface-active agents. P123 (PEO20–PPO65–PEO20) can remarkably enhance the retention of poorly soluble drugs in the blood circulation. Another important derivative of Pluronic, F127 (PEO100–PPO69–PEO100), possesses high biocompatibility. Therefore, mixed F127/P123 polymeric micelles have been developed, which have remarkably enhanced bioavailability with high encapsulation efficiency and low particle size. ISL-loaded F127/P123 polymeric micelles (ISL-FPM) improve the solubility as well as enhance the bioavailability and antioxidant activity of ISL [22].

- Nanoliposomes (NLs): Drug-loaded PEGylated nanomaterials have shown effective cancer cell-killing ability, PEG2000-DPSE-QUE-NLs (polyethyleneglycol-2000-distearoyl phosphatidyl ethanolamine loaded with quercetin (QUE)) can efficiently disperse in aqueous media compared to controls, and PEGylated (PEG2000-DPSE) NLs have been found to be effective drug delivery vehicles when simply loaded with ISL. ISL-NLs as tumor-targeted drug carriers are more effective in regulating glycolysis in colon cancer cell lines (CRC: HCT116)[23].

- Hydrogel: Hydrogels are composed of hyaluronic acid (HA) and hydroxyethyl cellulose (HEC), and they can improve the skin permeation of ISL[24].

As described above, many experiments have been conducted to evaluate the various properties of ISL nanoformulation have been developed to address the problems of bioavailability and solubility. Nanoformulation studies have been conducted in vitro and in vivo (Table 1), demonstrating that ISL nanoformulations improve the bioavailability by 2–10-fold[13][20][22].

**Table 1.** Nano-formulation of ISL.

| Formulation | Material | Particle Size (nm) | Model | Conclusion | Ref |
|---|---|---|---|---|---|
| Nanosuspension | Hydroxypropyl cellulose-SSL Polyvinylpyrroli-done-K30 | 238.1 ± 4.9 354.1 ± 9.1 | In vitro: A549 | HPC SSL-ISL-NS and PVP K30-ISL-NS both improve the solubility and cytotoxic activity of ISL ($IC_{50}$: ~0.08 μM). | [16] |
| Nanoencapsulation [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] | Mesoporous silica nanoparticles | ~200 | In vitro: mouse primary bone marrow-derived macrophages (BMMs) In vivo: lipopolysaccharide (LPS)-mediated calvarial bone erosion model (received 50 mg/kg MSNs-ISL; once every 2 days via subcutaneous injection) Experiment period: 7 days | MSNs-ISL as an effective natural product-based bone-bioresponsive nanoencapsulation system prevents osteoclast-mediated bone loss (In vitro effective dose: 16~64 μg/mL). | [34] [35] [17] |
| Lipid–polymer hybrid | ISL-iRGD nanoparticles | ~130 138.97 ± 2.44 | In vitro: MCF-7, MDA-MB231, 4T1 In vivo: 4T1-bearing nude mouse (received 35 μg/kg once every 2 days via IV injection) Experiment period: 20 days | RGD modified lipid–polymer hybrid NPs improve ISL in anti-breast cancer efficacy (Effective dose: >12 μM). | [18] |
| | LMWH-ISL-SLN | 217.53 ± 4.86 | In vitro: HepG2 In vivo: Kunming mice (6 female and 6 male; 50 mg/kg via IV injection daily) Experiment period: 14 days | Pharmacokinetics of LMWH-ISL-SLN demonstrated its safety and better bio-distribution after intravenous administration (In vitro $IC_{50}$: ~7.45 μg/mL). | [19] |
| Micro-emulsion | Self-microemulsifying drug delivery system (SEMDDS) | 44.78 ± 0.35 | In vivo: SD rat (oral administration: a single dose: 200 mg/kg) Experiment period: 24 h | ISL-SMEDDS can enhance the solubility and oral bioavailability of ISL. | [13] |

| Formulation | Material | Particle Size (nm) | Model | Conclusion | Ref |
|---|---|---|---|---|---|
| | | 20.63 ± 1.95 | In vivo: SD rat (oral administration: twice a day; 20 mg/kg) Experiment period: 63 days | | [25] |
| Nanostructured lipid carrier (ISL-NLC) | Monostearate and lecithin | 160.73 ± 6.08 | In vivo: Kunming mice bearing H22 and S180 tumor (intraperitoneal injection daily) Experiment period: 12 days | ISL-NLC nanoparticles with high envelopment efficiency with initial burst release, exhibiting superior in vivo antitumor effect and biodistribution. | [20] |
| | MS and Miglyol 812 | 160.73 ± 6.08 | In vivo: SD rat (oral administration: a single dose: 20 mg/kg) Experiment period: 36 h | NLC are valuable as an oral delivery carrier to enhance the absorption of a poorly water-soluble drug, ISL. | [15] |
| | Ceramide, cholesterol, caprylic/capric triglyceride | 150.2–251.7 | In vitro: Franz diffusion cell In vivo: ICR mice | NCL improved the skin permeation of ISL (permeability: 8.48~10.12 μg/cm$^3$). | [21] |
| TPGS-modified proliposomes | D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), proliposomes | 23.8 ± 0.9 | In vivo: Swiss-ICR mice oral administration Experiment period: 24 h | ISL-TPGS-PLP had small particle size, high encapsulation efficiency and drug loading capacity, and possessed good storage stability. | [14] |
| Polymeric micelles | ISL-loaded F127/P123 polymeric micelles (ISL-FPM) | 20.12 ± 0.72 | In vivo: SD rat, (oral administration: a single dose 200 mg/kg) Experiment period: 24 h | ISL-FPM act as a promising approach to improve solubility as well as enhance bioavailability and antioxidant activity of ISL. | [22] |
| Liposome | Phospholipid and cholesterol | 233.1 | In vitro: HeLa and SiHa | ISL liposome can significantly inhibit the proliferation of human cervical cancer cells in vitro. | [26] |

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**b**) EGFR;
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umor cell
nhibits the
e human
HEC-1A,
and RL95-2 cells). Their results indicated that ISL inhibits the growth of cancer cells at concentrations below 27 μM, but has little effect on normal cells[49]. Na et al. (2018) claimed that ISL shows little toxicity on normal hepatocyte cell lines (AML-12); only when applied in concentrations of over 100 μM is ISL harmful to normal

| [50] Formulation | Material | Particle Size (nm) | Model | Conclusion | Ref |
|---|---|---|---|---|---|
| Nanoliposome | Sodium cholate, cholesterol and IPM were melted with a ratio of 5:1:4 (w/w/w) | 82.3 ± 35.6 | In vitro: HCT116 and HT29 | ISL involved in the glucose metabolism in colon cancer. | [23] |
| Hydrogel systems | HA-HEC hydrogels | N.A. | In vitro: skin permeation study Franz diffusion cells | HA-HEC hydrogel showing the stable viscoelastic be haviour and the optimal adhesiveness has potential to enhance skin permeation of IS (permeability: 20 μg/cm$^3$). | [24] |

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ISL-derived n sues[27][28][29][30][31][32]. C its biological activity by modifying on the phenol ring to improve the performance of ISL. We summarized a few new analogues of ISL in below (see Figure 2).

**Figure 4.** Pharmacological effect of ISL. The scheme presents the biological effects of ISL and molecular mechanisms of ISL against cancer via various signal pathways.

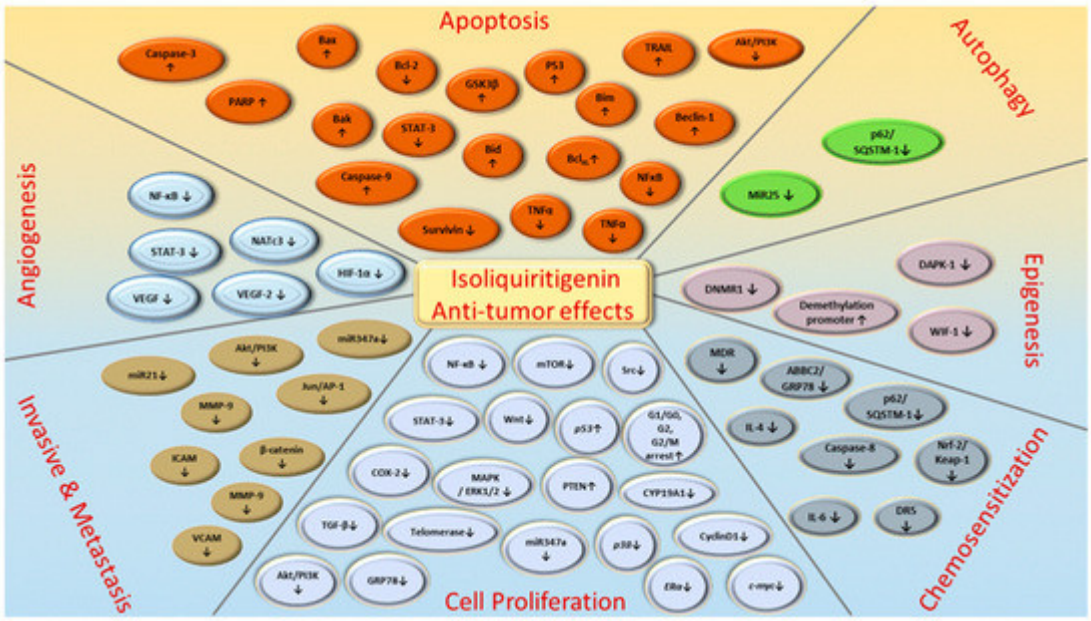


**Figure 5.** ISL-mediated regulation of molecular targets underlying anti-tumor effects, including tumor proliferation suppression, apoptosis induction, EMT/metastasis, epigenetic responses and sensitization to chemotherapy. Downward arrows (↓) represent downregulation while upward arrows (↑) represent upregulation. This figure was modified from[51].

**Figure 2.** Isoliquiritigenin (ISL) derivatives.

- 4-C-β-D-glucosylated ISL (Figure 2d): Glucosylation of low molecular weight compounds have improve water solubility and bioavailability with a good inhibition of aldose reductase (AR)[33].
- Synthetic isoliquiritigenin derivatives (BS5 and BS11, Figure 2b,c): The compounds BS5 and BS11 with m-, p-dimethoxy, o-bromo phenyl group shows neuroprotective effects at 3 μM to 6 μM with higher viability (~80–100%)[32].
- Robtein (ISL-derivative-10, Figure 2e): Robtein prohibited osteoclast differentiation and activation without any significant changes of viability or cytotoxicity[28].
- 2′,4′-dimethoxy-4-hydroxychalcone (Figure 2e): shows in vivo antidiabetic activity[31].
- 3′,4′,5′,4″-tetramethoxychalcone (TMC, Figure 2f): Introducing methylation of hydroxy groups significant increase cytotoxic activity in breast cancer[27], especially targeting on triple-negative breast cancer (TNBC)[29].
- ISL-17 (Figure 2g): A fluorine atom was introduced to the structure of ISL named ISL-17 showed the anti-tumor activities in gastric cancer[28].

However, the poor bioavailability and water-solubility issues remain in clinical applications. Future studies are still needed to elucidate the ISL formulations that would be more suitable for human clinical trials.

**Table 2.** ISL's influence on normal cell lines.

| Type | Cell Line | Result | Ref |
|---|---|---|---|
| Breast | MCF-10A (0~50 μM) (24 h) | ISL had no significant influence on MCF-10A as human normal tissues. | [36] |
| | MCF-10A (0~100 μM) (24 h) | ISL had limited inhibitory effect on the proliferation of normal cell and did not show the chemosensitization effect with epirubicin. | [52] |
| | H184B5F5/M10 (0.1~10 μM) (6~48 h) | ISL did not influence the normal cell viability at the at 0.1~10 μM. | [53] |
| Lung | HELF (24~72 h) | Both pure drug of ISL and nanosuspension showed low toxicity to normal cells. | [16] |
| Hepatocyte | AML-12 (0~200 μM) (24 h) | 5~50 μM of ISL increased cell proliferation, strong cytotoxicity was observed over 100 μM. | [50] |
| Uterus Endometrium | T-HESCs (5~100 μM) (24~48 h) | The viability of T-HESCs showed significant changes when ISL concentration over 75 μM was applied. | [49] |
| Gastric | GES-1 (20 μM) (48 h) | ISL exhibited a negligible effect on cell growth and cell viability exceeded 70%. | [28] |
| Endothelia | HUVEC | Over 10 μM of ISL is nontoxic with inhibiting the VCAM-1 and E-selectin. | [54] |
| Small intestine | IEC-6 (10~100 μM) (24 h) | No effect was observed in IEC-6 cells. | [55] |
| Oral | SG cell (25~400 μM) (24 h) | The half maximal effective dose ($IC_{50}$) of ISL is 386.3 ± 29.7 μM. | [56] |
| Brain | H22 | ISL had the potential to against glutamate-induced | [32] |

| Type | Cell Line | Result | Ref |
|---|---|---|---|
| | | neuronal cell death (neuroprotective effect) | |

**able 3.** Different pathways of various cancers regulated by ISL.

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| Breast cancer | MCF-7 | Testing conc: 10 nM~10 µM (5 days; 10 nM is sufficient) | • ⇧Presenilin2 (pS2) mRNA level<br>• ⇩Proliferation<br>• ⇩Estrogen receptor (ERα) | [57] |
| | MCF-7<br>MDA-MB-231 | Effective conc: 25 µM and 50 µM (24 h) | • ⇧WIF1<br>• ⇩DNMT1<br>• ⇩β-catenin (⇩Metastasis)<br>• ⇩Wnt<br>• ⇩G0/G1 (Cell cycle arrested)<br>• ⇩Cyclin D1 (⇧Apoptosis)<br>• ⇩Survivin<br>• ⇩c-myc<br>• ⇩Oct-4 | [41] |
| | MCF-7<br>MDA-MB-231<br>HUVEC | Testing conc.: 0, 20, 40, 60, 80, 100 µM<br>Tumor cell line: MCF-7 $IC_{50\ estimated}$ = ~33.39 µM MDA-MB-231 $IC_{50\ estimated}$ = ~35.64 µM (48 h) | • ⇧HIF-1α proteasome degradation<br>• ⇩VEGF expression<br>• ⇩Cancer growth via VEGF/VEGFR-2<br>• ⇩Neoangiogenesis via VEGF/VEGFR-2 | [58] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| Breast cancer | | HUVEC $IC_{50\ estimated}$ = ~75.48 μM | | |
| | PMA-induced COX-2 in MCF-10A | Effective conc: 0.1 μM and 10 μM (24 h; 1 μM is sufficient.) | • ⇩COX-2 expression modulated ERK-1/2 signaling | [59] |
| | BT549 MDA-MB-231 | Effective conc.: 10, 20, 40 μM (12 h) | • ⇧Cleaved caspase-3 & 9 (⇧Apoptosis)<br>• ⇩COX-2 (⇩Metastasis)<br>• ⇩CYP 4A, ⇩$PGE_2$, ⇩PLA2 | [60] |
| | MDA-MB-231 Hs-578T | Effective conc.: ~20 μM | • ⇧RECK<br>• ⇩miR21 and ⇩MMP-9 (⇩Invasive) | [61] |
| | | Testing conc.: 0, 5, 10, 20 μM | • ⇩mRNA level of phospholipase A2 (PLA2), cyclooxygenases-2 (COX-2) and cytochrome P450 (CYP) 4A | |
| | MCF-7 MDA-MB-231 | Tumor cell line: MCF-7 $IC_{50}$ = 10.08 μM MDA-MB-231 $IC_{50}$ = 5.5 μM (48 h) | • ⇩Cancer growth (⇩Arachidonic acid metabolism)<br>• ⇧Apoptosis<br>• ⇩PI3K/AKT pathway | [62] |
| | MCF-7 MDA-MB-231 | Testing conc.: 0, 6.25, 12.5, 25, 50, 100 μM | • ⇧PTEN (⇧Apoptosis)<br>• ⇧Bax (⇧Apoptosis)<br>• ⇧Caspase 9<br>• ⇧MMP-7 (⇩Lung metastasis) | [63] |
| | | Tumor cell line: MCF-7 $IC_{50}$: 32.66 μM | | |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | MDA-MB-231<br>Hs-578T | MDA-MB-231 $IC_{50}$: 22.36 µM<br>(24 h) | • ⇩miR374a (⇩Metastasis and ⇩proliferation)<br>• ⇩Bcl-2<br>• ⇩*p*-GSK3β, AKT<br>• ⇩β-catenin (⇩Migration and ⇩invasion)<br>• ⇧PIAS3<br>• ⇩miR21 and ⇩STAT3 (⇩Invasion) | [64] |
| | | Effective conc.: 10 µM and 20 µM | | |
| | | Testing conc.: 1, 5, 10 and 25 µM | • ⇧Proteasome degradation<br>• ⇧β-catenin degradation | |
| | MCF-7<br>MDA-MB-231<br>BT549<br>MCF-10 | Tumor cell lines:<br>MCF-7 $IC_{50\ estimated}$: ~33.0 µM<br>MDA-MB-231 $IC_{50\ estimated}$: ~21.2 µM<br>BT549 $IC_{50\ estimated}$: ~18.1 µM<br>(24 h) | • ⇧Apoptosis via ⇩ miR-374a<br>• ⇧Chemosensitivity<br>• ⇩β-catenin /ABCG2/ GRP78 (⇩Proliferation)<br>• ⇩GSK-3β phosphorylation via AKT pathway (⇧Chemosensitization) | [36] |
| | | Normal cell line:<br>MCF- 10A $IC_{50\ estimated}$: ~80.51 µM<br>(24 h) | • ⇩$CD44^{+}CD24^{-}$, Survivin, Oct-4,<br>• ⇩Cyclin D1 | |
| Breast cancer | MCF-7<br>MDA-MB-231<br>H184B5F5/M10 | Effective conc: 25 µM and 50 µM<br>(48 h) Tumor cell lines:<br>MCF-7<br>MDA-MB-231 | • ⇩VEGF (⇩Anti-angiogenesis)<br>• ⇩HIF-1α (⇩Proliferation)<br>• ⇩MMP-9 (⇩Migration)<br>• ⇩PI3K | [65] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | | Normal cell line: H184B5F5/M10 (ISL did not influence the viability) | • ⇩NF-kB<br>• ⇩p38 | |
| | MCF-7<br>MCF-7/ADR<br>MCF-10A | Tumor cell lines: MCF-7 $IC_{50\ estimation}$: ~59.39 μM MCF-7/ADR $IC_{50\ estimation}$: ~38.86 μM (24 h) | • ⇧ULK1 (⇧Autophagy)<br>• ⇧LC3-II (⇧Chemosensitization)<br>• ⇩miR-25(⇧Autophagy)<br>• ⇩ABCG2 | [53] |
| | | Normal cell line: MCF-10A ISL (at 100 μM) had limited inhibitory effects on the proliferation | | |
| | MDA-MB-231 | Testing conc.: 0, 10, 25, 50 μM MDA-MB-231 $IC_{50\ estimated}$: ~24.23 μM (48 h) | • ⇧Bax<br>• ⇧Caspase-3 and ⇧PARP<br>• ⇧ p62, ⇧Beclin1, and ⇧LC3 (⇧Autophagy)<br>• ⇧Caspase-8 (⇧Autophagy and ⇧apoptosis)<br>• ⇩Cyclin D1 (⇩Proliferation)<br>• ⇩Bcl-2<br>• G1 arrest | [66] |
| | MCF-7aro | Testing conc.: 0, 0.625, 1.25, 2.5, 5, 10 μM MCF-7aro $IC_{50}$: 2.5 μM (24 h) | • ⇩mRNA level of aromatase<br>• ⇩CYP19 promoters I.4, I.3 and II activity | [44] |
| Colon cancer | HT29 | HT29 $ED_{50}$: 11.1 μg/mL (42.32 μM) | • DNA demethylating effect | [67] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | HT29 | Testing conc.: 0, 5,10, 20, 30, 40, 50 µM<br>40 µM was applied; (24 h) | • ⇧DR5(⇧Apoptosis)<br>• ⇩PI3K/AKT pathway | [68] |
| | HCT116<br>HT29<br>SW480 | Testing conc.: 0,10, 20, 30, 40 µM<br>HCT116 $IC_{50\ estimated}$ = ~42.41 µM<br>Working conc.: 30 or 40 µM; (24 h) | • ⇧Apoptosis<br>• ⇧p62/SQSTM1 (⇧Autopage cell death)<br>• ⇧PARP cleavage<br>• ⇩Caspase-8 activation (⇧Apoptosis) | [69] |
| | HCT116 | Testing Conc.: 0, 2.5,5, 10, 20, 40, 80, 160 µM<br>HCT116 $IC_{50\ estimated}$: ~78.78 µM (48 h)<br>HCT116 $IC_{50\ estimated}$: ~53.97 µM (72 h)<br>HCT116 $IC_{50\ estimated}$: ~44.8 µM (96 h) | • ⇧NAG-1 expression mediated EGR-1, p53, ATF-3, Sp1 and PPARγ<br>• ⇧Apoptosis (Caspase dependent pathway)<br>• ⇩Bcl-2 and Bcl-$x_L$<br>• G2 phase cycle arrested | [70] |
| | CT26 | Testing Conc.: 0, 10, 20, 40, 60, 80 µM<br>CT26 $IC_{50\ estimated}$ = ~54.48 µM | • ⇧Serum nitric oxide, ⇧Lipid peroxidation levels and ⇧GSH levels<br>• ⇩ ROS<br>• ⇩Proliferation<br>• ⇩COX-2 (⇧Apoptosis) | [71] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| Colon cancer | Colon26<br>RCN9<br>CoLo-320DM | Testing Conc.: 0, 5, 25, 100 µM (24, 48 h)<br>Colon26 $IC_{50\ estimated}$ = ~17.55 µM (24 h)<br>Colon26 $IC_{50\ estimated}$ = ~12.59 µM (48 h)<br>RCN9 $IC_{50\ estimated}$ = ~41.73 µM (24 h)<br>RCN9 $IC_{50\ estimated}$ = ~18.21 µM (48 h)<br>CoLo-320DM $IC_{50\ estimated}$ = ~23.10 µM (24 h)<br>CoLo-320DM $IC_{50\ estimated}$ = ~10.82 µM (48 h) | • ⇧Apoptosis<br>• ⇩$PGE_2$ depends on ⇩COX-2 expression<br>• ⇩NO via (⇩iNOS) | [72] |
| | HCT116 | Applied 20 µM (48 h) | • ⇧Bax and ⇧cleaved caspase-3 (⇧Apoptosis)<br>• ⇩PI3K/AKT signaling pathway<br>• ⇩Cancer proliferation, ⇩Invasion and ⇩migration<br>• ⇩Bcl-2, *p*-AKT, *p*-mTOR, CyclinD1 | [73] |
| | Caco-2/TC-7 | Caco-2/TC-7 $EC_{50}$: 42 µM | • ⇧ HBD3 (human β-defensin-3)<br>• ⇧EGFR-MAPK pathway | [74] |
| Ovary cancer | SKOV3<br>OVCAR5<br>ES2 | Testing conc.: 2, 4, 8, 16, 32, 64, and 100 µM<br>SKOV3 $IC_{50}$: 83.2 µM (72 h)<br>OVCAR5 $IC_{50}$: 55.5 µM (72 h)<br>ES2 $IC_{50}$: 40.1 µM (72 h)<br>Effective Conc.: 10 µM | • ⇧E-cadherin<br>• ⇩ZEB1 mRNA<br>• ⇩Vimentin and ⇩N-cadherin (⇩EMT)<br>• ⇩TGF-*β* | [75] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | SKOV3<br>OVCAR5 | Testing conc.: 0, 1, 5, 10, 20, 25, 50, 75, and 100 μM<br>OVCAR5 $IC_{50}$: 11 μM (48 h)<br>ES2 $IC_{50}$: 25 μM (48 h) | • ⇧Cleaved PARP, ⇧cleaved caspase-3, ⇧ Bax/Bcl-2 ratio, ⇧LC3B-II, and ⇧Beclin-1<br>• ⇧CDK2<br>• G2/M phase arrest<br>• ⇩Cyclin B1 | [76] |
| | Antral follicle culture (female CD-1 mic) | Testing conc.: 0.6, 6, 36, and 100 μM | • ⇧STAR<br>• ⇩mRNA levels of cytochrome P450 steroid 17 α-hydroxylase 1 (⇩CYP17A1), cytochrome P450 aromatase (⇩CYP19A1) | [77] |
| | SKOV3<br>OVCAR3 | Testing conc.: 5~80 μM<br>30 μM applied | • ⇧GSK3β<br>• ⇩*p*-AKT and *p*-mTOR<br>• ⇩P70/S6K, Cyclin D1<br>• ⇩Wnt3a, ⇩p-ERK, ⇩PI3K/AKT/mTOR | [78] |
| | SKOV3 | N.A. | • ⇧ER stress,⇧ *p*-eIF2α, GADD153/CHOP, GRP78, XBP1 expression, and cleavage of ATF6α (⇧Apoptosis and ⇧autophagy) | [76]<br>[79] |
| Lung cancer | H1299<br>H1975<br>A549 | H1299 $IC_{50\ estimated}$: ~36.78~46.08 μM<br>H1975 $IC_{50}$: 48.14 μM<br>A549 $IC_{50}$: 75.08 μM (48 h) | • ⇩Src kinase activity (⇩Proliferation and ⇩migration) | [9] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | A549 | A549: applied 20 μM (24 h) | • ⇧Bax and ⇧caspase-3<br>• ⇧E-cadherin<br>• ⇩Bcl-2<br>• ⇩mTOR (⇩PI3K/AKT pathway)<br>• ⇩P70, ⇩Cyclin D1, ⇩*N*-cadherin and ⇩vimentin | [80] [81] |
| | RAW 264.7 | Testing conc.: 5, 10, 20 μM for (Pretreated with 10mM of t-BHP for 18 h) RAW 264.7 (treated with t-BHP) $EC_{50}$ = 10 μM (18 h) | • ⇧AMPK/Nrf2 signaling<br>• ⇧ Nrf2 and its target enzymes (e.g., ⇧HO-1, ⇧GCLM, ⇧GCLC, and⇧ NQO1)<br>• ⇩iNOS and ⇩COX-2<br>• ⇩TNF-α, ⇩IL-1β, and ⇩IL-6<br>• ⇩NLRP3 in a Nrf2-dependent pathway<br>• ⇩NF-κB (p65) via Nrf2-independent pathway | [82] |
| | Calu-3 | Calu-3 cells were infected with PR8/H1N1 virus; [$EC_{50}$] = 24.7 μM | • ⇧PPARγ (⇩Influenza virus infection)<br>• ⇧TNF-α, ⇧IL-1β, and ⇧IFN-β | [83] |
| | H1650<br>H1975<br>A549 | H1650 $IC_{50\ estimated}$: ~26.88 μM (24 h) H1975 $IC_{50\ estimated}$: ~8.92 μM (24 h) A549 $IC_{50\ estimated}$: ~46.7 μM (24 h) | • ⇧Bim (⇧Apoptosis)<br>• ⇩Bcl-2, ⇩ *p*-AKT, and ⇩*p*-ERK1/2 | [38] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | A549 | A549 $IC_{50}$: 0.05 mg/mL (~191.21 μM ~117 μM) | • ⇧p53, ⇧p21 and ⇧Bax<br>• Arrest at G2/M phase<br>• ⇩PCNA, ⇩ MDM2, ⇩*p*-GSK-3β, ⇩*p*-AKT, ⇩*p*-c-Raf, ⇩*p*-PTEN, ⇩caspase-3, ⇩pro-caspase-8, ⇩pro-caspase-9, ⇩PARP, and ⇩Bcl-2 | [84] |
| Lung cancer | guinea-pig tracheal smooth muscle | N.A. | • ⇧cGMP/PKG (⇧BKCa channels opened)<br>• ⇩PDEs (⇩$[Ca^{2+}]_i$ led tracheal relaxation) | [85] |
| | A549 | A549 $IC_{50}$: 27.14 μM | • ⇧p53 and ⇧p21/WAF1<br>• ⇧Apoptosis via Fas/FasL apoptotic system<br>• Arrested at G1 phase (⇩Proliferation) | [86] |
| | A549 | A549 $IC_{50}$: 18.5 μM | • ⇧$p21^{CIP1/WAF}$ via p53 independent pathway<br>• G2/M arrest(⇩Proliferation) | [87] |
| AML (acute myeloid leukemia) | HL-60 | HL-60 $ED_{50}$: 5.5 μg/mL (~21.46 μM) 5.00 μg/mL = 19.5 μM (72 h) | • ⇧DNA demethylation | [61] |
| | MV4-11 MOLM-13 OCI-LY10 | MV4-11 $IC_{50}$: 3.2 + 1.2 μM; MOLM-13 $IC_{50}$: 4.9 + 2.1 μM OCI-LY10 $IC_{50}$: | • ⇧STAT5<br>• ⇩FLT3/Erk1/2 | [31] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | | 20.1 ± 6.7 μM (72 h) | | |
| | LCLs | Testing conc.: 0, 20, 40, 60, 80, 100, 120, 140 μM LCLs $IC_{50\ estimated}$: 40~65 μM (24 h) Applied 50 μM for studies. | • ⇧HMOX1, ⇧SLCO2B1, and⇧OKL38<br>• ⇩CDK5R1 and CDC45L via p53 pathway | [80] |
| | HL-60 | Testing conc.: 1~15 μg/mL (3.9 μM~58.54 μM) HL-60 $IC_{50\ estimated}$: ~40.42 μM (72 h) | • ⇧CD11b and ⇧CD14 expression (⇩Proliferation)<br>• ⇩iROS (⇧monocytic differentiation) | [81] |
| | RAW264.7 | Testing conc.: 20 and 50 μM | • ⇩TRIF-dependent pathway<br>• ⇩NF-κB and ⇩IRF3 | [88] |
| AML (acute myeloid leukemia) | RAW264.7 | Testing conc.: 50 and 100 μM | • ⇧IRF3<br>• ⇩TBK1 kinase activity<br>• ⇩IFNβ production | [89] |
| | HL-60 | Testing conc.: 2.5~20 μg/mL (3.9 μM~78.05 μM) (Working conc.: 72 μM) | • ⇧CD11b and ⇧CD14 mRNA expression<br>• ⇧gp91phox and ⇧p47phox<br>• ⇧NADPH oxidase (⇩ROS)<br>• ⇩ROS (⇧HL-60 differentiation) | [90] |
| | HL-60 | Testing conc.: 2.5~10 μg/mL (3.9 μM~39.0 μM) | • ⇧CD11b and ⇧CD14 (⇧Monocyte differentiation via Nrf2/ARE) | [91] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | | | • ⇧Horseshoe-shaped nuclei<br>• ⇧Lipid peroxidation (MDA) level<br>• ⇩GSH/GSSG ratio (mRNA expression of ⇧CAT, ⇧NQO-1, ⇧Thioredoxin reductase and ⇧TRx) | |
| | Jurkat<br>J-Jhan<br>J16<br>HUT78<br>Karpas 45 | Jurkat $IC_{50}$: 0.49 ± 0.12 nM (72 h)<br>J-Jhan $IC_{50}$: 1.55 ± 1.12 nM (72 h)<br>J16 $IC_{50}$: 5.25 ± 1.12 μM (72 h)<br>HUT78 $IC_{50}$: 11 ±13.5 μM (72 h)<br>Karpas 45 $IC_{50}$: 6.61 ± 1.07 μM (72 h) | • ISL did not have a correlation with doxorubicin (DOX) and methotrexate (MTX) in genomic profiles.<br>• ISL is a valuable adjunct for cancer therapy, especially targeting on drug-resistant tumors. | [92] |
| | CCRF-CEM | CCRF-CEM $IC_{50}$: 18.38 μM (24~72 h) | • ⇩Mitochondrial membrane potential disruption<br>• ⇧DNA damage<br>• G2/M arrest (⇩Proliferation)<br>• ⇩Cytochrome c | [93] |
| AML (acute myeloid leukemia) | Human monocyte model THP-1 | N.A. | • ⇧DNCB-induced MAPK activation<br>• ⇧CD86 and ⇧CD54<br>• ⇩DNCB-induced pro-inflammatory cytokines (⇩TNF-α, ⇩IL-6 and ⇩IL-4)<br>• ⇩p38-α and ⇩ERK activation | [94] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| Melanoma | A375<br>A2058 | Testing Conc: 0, 10, 20, 40,<br>80 μM<br>A375 $IC_{50}$: 21.63 μM (24 h)<br>A2058 $IC_{50}$: 20.75 μM (24 h) | • ⇧C-PARP, ⇧Bax, ⇧ cleaved-caspase-3(⇧Apoptosis)<br>• ⇩Proliferation<br>• ⇩Bcl-2 | [95] |
| | B16F0 | N.A. | • ⇧B16F0 differentiation | [96] |
| | A375 | Testing Conc.: 0, 5, 10, 15 μg/mL<br>(15 μg/mL = 58.53 μM)<br>A375 $IC_{50\ estimated}$: ~48 μM | • ⇧Melanin content (⇧Melanogenesis)<br>• ⇧Tyrosinase (TYR) activity<br>• ⇧$O_2$ consumption rate (OCR)<br>• G2/M cell cycle arrest<br>• ⇩mRNA level of GLUT1 and HK2<br>• ⇩mTOR, ⇩*p*-mTOR, ⇩RICTOR, ⇩*p*-AKT, ⇩*p*-GSK3β | [97] |
| | A375 | 40 μg/mL: 69.86%<br>60 μg/mL: 92.22%<br>A375 $IC_{50\ estimated}$: ~73 μM (24 h) | • ⇧Cleaved PARP and ⇧Cleaved caspase-3<br>• ⇩Mitochondrial membrane potential<br>• ⇩mitoNEET | [98] |
| Melanoma | B16F0 | Testing Conc.: 20, 40, 60 and<br>80 μg/mL<br>B16F10 $IC_{50\ estimated}$: 35 μg/mL<br>(~41.576 μM; 24 h)<br>B16F10 $IC_{50\ estimated}$: 22 | • ⇧ROS (⇧Apoptosis)<br>• Restart TCA cycle<br>• ⇩HIF-1α (Alleviating hypoxia) | [99] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | | µg/mL (~86.77 µM; 48 h) | • ⇩Lactate production<br>• ⇩Glucose uptake and glycolysis | |
| | B16F10 | Testing Conc.: 5, 10, 15, 20, and 25 µg/mL<br>B16F10 $IC_{50\ estimated}$: ~19 µg/mL (~74.595 µM; 24 h)<br>B16F10 $IC_{50\ estimated}$: ~10.5 µg/mL (~41.576 µM; 48 h) | • ⇧TYR Activity<br>• ⇧Melanin Biosynthesis<br>• ⇧ROS<br>• ⇩Colony formation<br>• ⇩Cell proliferation | [100] |
| | ARH-77<br>U266<br>MPC-11 SP2/0<br>CZ-1<br>RPMI8226 | ARH-77 $IC_{50}$: ~13.54 µM<br>MPC-11 $IC_{50}$: ~4.45 µM<br>SP2/0 $IC_{50}$: ~22.91 µM<br>CZ-1 $IC_{50}$: ~13.93 µM<br>U266 $IC_{50}$: ~8.62 µM<br>RPMI8226 $IC_{50}$: ~9.09 µM<br>$IC_{50}$ of ISL was < 4 µg/mL (48 h) | • ⇧Cleavage caspase-3<br>• ⇩IL-6<br>• ⇩p-ERK and ⇩*p*-STAT3<br>• ⇩Bcl-2, ⇩Bcl-XL and ⇩pro-caspase-3 | [101] |
| | SK-MEL-2<br>HaCaT | Testing Conc.: 0, 1, 4, and 8 µM<br>SK-MEL-2 cells and HaCaT cells (48 h) treated less than 8 µM showed no cytotoxic effects | • ⇧p-p38<br>• ⇩Tyrosinase (⇩Tyrosine kinase)<br>• ⇩ TRP-1, ⇩DCT, ⇩Rab27a and ⇩Cdc42<br>• ⇩ ERK pathway (⇩Degradation of MITF) | [102] |
| Melanoma | B16 mouse melanoma 4A5 cells | Testing 150 and 200 µM (18 and 24 h) | • ⇧Apoptosis (p53 independent pathway)<br>• ⇧Bax | [103] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | | | • ⇩Cell proliferation<br>• ⇩Glucose transmembrane transport | |
| HCC/Hepato-ma | Hep3B | Hep3B $IC_{50}$: 42.84 + 2.01 μM<br>50 μM applied (48 h) | • ⇧P21, ⇧P27<br>• G1/S cell cycle arrest (⇩Proliferation)<br>• ⇩Cyclin D1<br>• ⇩PI3K/AKT pathway<br>• ⇧E-cadherin, ⇩Vimentin and ⇩N-cadherin (⇩Migration and ⇩metastasis) | [104] |
| | HepG2<br>Hep3B | Testing conc.: 20, 40, 60, 80, and 100 μM (18 h)<br>HepG2 $IC_{50}$: 27.71 μM<br>Hep3B $IC_{50}$: 35.28 μM | • ⇧ MAPK/STAT3/NF-κB (⇧Apoptosis)<br>• ⇧ ROS accumulation<br>• ⇧Phosphorylated c-Jun N-terminal kinase (JNK), ⇧P21, ⇧p38 kinase<br>• G2/M arrest (⇩Proliferation)<br>• ⇩p-ERK, ⇩p-STAT3, and ⇩NF-κB (p65)<br>• ⇩Cyclin B1, ⇩CDK1/2, and ⇩p27 | [105] |
| | HepG2 | Testing conc.: 1, 5, 10, 20 μg<br>HepG2 $IC_{50\ estimated}$: ~88.46 μM (24 h)<br>HepG2 $IC_{50\ estimated}$: ~31.07 μM (48 h) | • ⇧p53, ⇧p21/WAF1, ⇧ Fas/APO-1 receptor, Fas ligand, ⇧Bax and ⇧NOXA (⇧Chemopreventive effect) | [106] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | | | • G2/M-phase arrest | |
| | HepG2 | HepG2 $IC_{50}$: 10.51 μg/mL (~39 μM; 48 h) | • ⇧IkB<br>• ⇩NF-κB, Bcl-$X_L$, c-IAP1/2 | [107] |
| | SNU475 | SNU475 $IC_{50}$: 0.243 + 0.21 mM | • ⇩ DNA cleavage reaction (Stabilized DNA)<br>• ⇩TOP I activity(ISL-TOP I interaction: 0.18 + 0.12 mM) | [58] |
| HCC/Hepato-ma | Hepa 1c1c7 | Hepa 1c1c7 $IC_{50}$: 36.3 μM | • ISL is a chemopreventive reagent | [108] |
| | Hep3B | Hep3B $IC_{50}$: 50.8 μM | • ⇩CK2 activity (CK2 $IC_{50}$: 17.3 uM) | [43] |
| | SK-Hep-1 | SK-Hep-1 $IC_{50}$: 19.08 μM | • ⇩ Proliferation | [109] |
| | PC-3<br>22RV1 | Testing conc: 0, 1, 10, 25, 50, and 100 μM)<br>PC-3 $IC_{50}$: 19.6 μM (48 h)<br>22RV1 $IC_{50}$: 36.6 μM (48 h) | • ⇧Apoptosis<br>• G2/M cell cycle arrest<br>• ⇩Cyclin B1, ⇩CDK1 (p-Thr14, p-Tyr15, and p-Thr161) | [110] |
| Prostate cancer | C4-2<br>LNCaP<br>IEC-6 | 10~100 μM (24 h)<br>C4-2 $IC_{50}$: 87.0 μM | • ⇧AMPK and ⇧pERK (⇩Proliferation)<br>• ⇧*p*-p38<br>• ⇩Psi(m) (⇧Apoptosis) | [59] |
| | DU145 | Applied conc.: 5~20 μM | • ⇧*p*-CDC2 (Tyr15) and ⇧Cyclin B1 | [111] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | | | • ⇧G1 phase<br>• ⇧$p27^{KIP1}$<br>• G2/M cell cycle arrest<br>• ⇩CDC25C | |
| | DU145 | Applied conc.: 0~20 μM | • ⇩JNK/AP-1 signaling<br>• ⇩VEGF, ⇩integrin-α2, ⇩ICAM and ⇩VCAM<br>• ⇩Invasion and ⇩metastasis via ⇩μPA, ⇩MPP-9 and ⇩AP-1 | [112] |
| | DU145 | Applied conc.: 0~20 μM | • ⇩PI3K/AKT and ErbB3 pathway (⇩Proliferation)<br>• ⇩HRG-β-induced ErbB3 signaling (⇩ErbB3) | [113] |
| Prostate cancer | MAT-LyLu<br>DU145 | Applied conc.: 0~20 μM<br>MAT-LyLu$IC_{50\ estimated}$: ~13.74/5.67/5.01 μM<br>DU145 $IC_{50\ estimated}$: ~56.87/31.49/17.60 μM (24 h/48 h/72 h) | • ⇧ Fas ligand (FasL), ⇧Fas, ⇧Cleaved caspase-8 and ⇧tBid (⇧Apoptosis)<br>• lic>249) ⇧Cytochrome c and Smac/Diablo | [114] |
| | DU145 LNCaP | Testing conc.: 0, 5, 10, 15, and 20 μM<br>DU145 $IC_{50\ estimated}$: ~10.561 μM (48 h)<br>LNCaP $IC_{50\ estimated}$: ~10.775 μM (48 h) | • ⇧GADD153 mRNA<br>• S and G2/M arrest | [115] |
| Cervical cancer | Ca Ski<br>SiHa<br>HeLa<br>C-33A | Testing conc: 10, 20, 40, and 80 μM<br>Ca Ski $IC_{50\ estimated}$: 39.09 μM (72 h) | • ⇧p53, ⇧p21, ⇧Bax | [116] |

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | | SiHa $IC_{50\ estimated}$: 53.76 μM (72 h)<br>HeLa $IC_{50\ estimated}$: 58.10 μM (72 h)<br>C-33A $IC_{50\ estimated}$: 32.83 μM (72 h) | • ⇧Cleavage of caspase-9, ⇧caspase-3, ⇧PARP and ⇧caspase -8<br>• ⇩Bcl-2 | |
| | HeLa | Testing conc: 2, 5, 10, 30, 40, and 60 μg/mL<br>HeLa $IC_{50\ estimated}$: ~21.24 μM (24 h) | • ⇧ROS<br>• ⇧*p*-eIF2α, ⇧GRP78 level (⇧ER stress)<br>• ⇧Caspase-12<br>• G2/M cell cycle arrest (⇩Proliferation)<br>• ⇩Bcl-2 | [117] |
| | HeLa | HeLa $IC_{50}$: 9.8 μM (48 h) | • ⇧p53<br>• ⇧*p*-Chk2, ⇧*p*-cdc25C, and ⇧*p*-cdc2<br>• G2/M cell cycle arrest<br>• ⇩*p*-p53 (Serine15)<br>• ⇩Bcl-2, Bcl-XL<br>• ⇩Cyclin B, ⇩cyclin A, ⇩cdc2, and ⇩cdc25C | [118] |
| Gastric cancer | MKN28 | MKN28 $IC_{50}$: ~20.84 μM (48 h) | • ⇧Beclin 1<br>• ⇩p62 (⇧Autophagy) | [119] |

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| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | | | • ⇩*p*-AKT and ⇩*p*-TOR (⇧Apoptosis) | |
| | MKN-45 | 5 μM applied | • ⇩H2R and ⇩c-Fos/c-Jun | [120] |
| | MGC-803 | 0.11 g/L applied (24 h) | • Calcium- and delta psi(m)-dependent (⇧Apoptosis) | [121] |
| | SGC-7901<br>BGC-823 | BGc-823 $IC_{50}$: 23.18 μM (48 h)<br>SGC-7901 $IC_{50}$: 12.91 μM (48 h) | • ⇧G2/M cell cycle arrest (⇩Proliferation)<br>• ⇧Cleaved-PARP, ⇧Bcl-2 and ⇧Bax (⇧Apoptosis)<br>• ⇧LC3B II and⇧ Beclin 1(⇧Autophagy)<br>• ⇩PI3K/AKT/mTOR | [34] |
| Uterine leiomyoma | Leiomyma<br>Myomentrium | Testing conc: 0, 10, 20, 50 μM<br>Leiomyma $IC_{50\ estimated}$ = ~39.33 μM<br>Myomentrium $IC_{50\ estimated}$ = ~698.8 μM (48 h) | • ⇧FAS ligand expression(⇧Apoptosis)<br>• ⇧$p21^{Cip1/\ Waf}$ (⇧Apoptosis via p53-dependent)<br>• ⇧Caspase-3 activation<br>• subG1 and G2/M arrest (⇩Proliferation)<br>• ⇩Bcl-2, ⇩cdk 2/4, and ⇩E2F | [122] |
| Osteosarcoma | U2OS | Testing conc: 5, 10, and 20 μM<br>20 μM applied | • ⇧Bax and ⇧caspase-3 (⇧Apoptosis)<br>• ⇧p53, ⇧p21 and ⇧p27 | [123]<br>[128] |

Enhances Cytostatic Ef-fects in A549 Lung Cancer Cells. Planta Med. 2020, 86, 538–547, doi:10.1055/a-1134-3378.

| Type of Cancer | Cell | Testing Range/$IC_{50}$ | Signaling Pathways Effect of ISL (In Vitro) | Ref |
|---|---|---|---|---|
| | Saos-2<br>MC3T3-E1 | Saos-2 $IC_{50\ estimated}$ = ~24.23 μM<br>30 μM applied | • ⇩Bcl2, ⇩PI3K/AKT/mTOR pathway<br>• ⇩p70, ⇩Cyclin D1, ⇩Bcl-2, ⇩MMP-2/⇩MMP-9 | |
| Glioma | SK-N-BE(2)<br>IMR-32 | Effective conc. > 5 μM | • ⇧ROS (⇧Necrosis) | [125] |
| | U87 | U87 $IC_{50}$: 6.3 μM | • ⇧Caspase-3<br>• ⇩TOP I | [124] |
| | PC12 | PC12 $IC_{50}$: 17.8 ± 1.8 μM | • ⇧Caspase-9, ⇧caspase-3, ⇧caspase-7, ⇧Bax, ⇧Bim, and ⇧cytochrome c (⇧Apoptosis)<br>• ⇧Beclin-1 and ⇧LC3 (⇧Autophagy) ⇩Bcl-2 and ⇩Bcl-x | [126] |
| Bladder cancer | T24 | Effective conc.: 30 and 70 μg/mL<br>(24 h) | • ⇧Bax, ⇧Bim, ⇧Apaf-1, ⇧Caspase-9, ⇧Caspase-3, and ⇧CDK2 activity<br>• ⇩ΔΨm and ⇩Bcl-2 | [127] |
| Oral squamous cell carcinomas (OSCC) | SG<br>SAS-CSCs<br>OECM-1 | SG cells $IC_{50}$: 386.3 ± 29.7 μM<br>SAS-CSCs $IC_{50}$: 144.9 ± 25.7 μM<br>OECM-1-CSCs $IC_{50}$: 104.5 ± 26.2 μM | • ⇩GRP78<br>• ⇩CSCs properties<br>• ⇩ABCG2 expression | [54] |

Note: The "$IC_{50}$ estimated" indicated Data extracted from published figures using Web Plot Digitizer (https://automeris.io/WebPlotDigitizer), then analyzed $IC_{50}$ by "Quest Graph™ $IC_{50}$ Calculator." AAT Bioquest Inc, 27 October 2020, https://www.aatbio.com/tools/ic50-calculator [133].


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