HHS Public Access

Author manuscript

Eur J Pharmacol. Author manuscript; available in PMC 2020 June 05.

Published in final edited form as:

Eur J Pharmacol. 2019 June 05; 852: 107–124. doi:10.1016/j.ejphar.2019.02.022.

Anticancer and antimetastatic potential of enterolactone: Clinical, preclinical and mechanistic perspectives

Aniket V. Mali[a,b], **Subhash B. Padhye**[c,d], **Shrikant Anant**[d], **Mahabaleshwar V. Hegde**[a,*], **Shivajirao S. Kadam**[b]

[a]Center for Innovation in Nutrition Health and Disease (CINHD), Interactive Research School for Health Affairs (IRSHA), Bharati Vidyapeeth (Deemed to be University), Dhankawadi, Pune, Maharashtra 411043, India

[b]Pharmaceutical Sciences, Poona College of Pharmacy, Bharati Vidyapeeth (Deemed to be University), Pune, Maharashtra 411038, India

[c]Interdisciplinary Science and Technology Research Academy, Abeda Inamdar College, University of Pune, Pune 411001, India

[d]Cancer Biology, University of Kansas School of Medicine, Kansas City, KS 66160, USA

Abstract

Currently cancer is the second leading cause of death globally and worldwide incidence and mortality rates of all cancers of males and females are rising tremendously. In spite of advances in chemotherapy and radiation, metastasis and recurrence are considered as the major causes of cancer related deaths. Hence there is a mounting need to develop new therapeutic modalities to treat metastasis and recurrence in cancers. A significant amount of substantiation from epidemiological, clinical and laboratory research highlights the importance of diet and nutrition in cancer chemoprevention. Enterolactone (EL) is a bioactive phenolic metabolite known as a mammalian lignan derived from dietary lignans. Here in we review the reported anti-cancer properties of EL at preclinical as well as clinical level. Several in-vivo and in-vitro studies have provided strong evidence that EL exhibits potent anti-cancer and/or protective properties against different cancers including breast, prostate, colorectal, lung, ovarian, endometrial, cervical cancers and hepatocellular carcinoma. Reported laboratory studies indicate a clear role for EL in preventing cancer progression at various stages including cancer cell proliferation, survival, angiogenesis, inflammation and metastasis. In clinical settings, EL has been reported to reduce risk, decrease mortality rate and improve overall survival particularly in breast, prostate, colon, gastric and lung cancer. Further, the in-vitro human cell culture studies provide strong evidence of the anticancer and antimetastatic mechanisms of EL in several cancers. This comprehensive

*Corresponding author. mahabaleshwar.hegde@bharatividyapeeth.edu, mahabaleshwarh@yahoo.com (M.V. Hegde).

Author contributions

All authors contributed to the study design, planning and data extraction. **AVM** drafted the initial manuscript. **MVH** and **SSK** revised the initial manuscript. All authors have seen and approved the final draft. Final editing of the manuscript was carried out by **SBP** and **SA**. All authors have seen and approved the final draft.

Conflict of interest

This work was supported by an institutional funding. Authors declared no potential conflicts of interest.

review supports an idea of projecting EL as a promising candidate for developing anticancer drug or adjunct dietary supplements and nutraceuticals.

Keywords

Enterolactone; Anticancer; Dietary Lignans; Mammalian Lignans; Anti-metastatic activity; Flax seeds

1. Introduction

Cancer is considered as the second leading cause of death globally according to WHO statistics and was responsible for 8.8 million deaths in 2015 (Global Burden of Disease Cancer Collaboration, 2017). As per GLOBOCAN 2012 data (Ferlay et al., 2015), there are 14 million new cancer cases per year which is expected to rise to 24 million new cases by 2035. The number of cancer-related deaths are also expected to rise from 8.2 million to 14.6 million annually (Stewart et al., 2016). The International Agency for Research on Cancer (IARC) estimated that the worldwide incidence and mortality rates of all cancers of males and females are very high in United States of America (USA), European Union (EU) and other developed regions (Ervik et al., 2016). As indicated in GLOBOCAN 2012 data based on incidence, mortality and prevalence worldwide in both sexes, the top 5 most frequent cancers occur in the lung, breast, colorectum, prostate and stomach tissues. Moreover, incidence and mortality rates of other cancers such as liver and bladder cancer in men and cervical, endometrial and ovarian cancer in females are also rising (Ferlay et al., 2015). Metastasis and recurrence are considered as the major causes of cancer related deaths in spite of advances in chemotherapy and radiation (Qian et al., 2017). Patients with metastatic tumors in all types of cancer are often unresponsive to existing therapies and strategies to achieve long-term remission than patients with localized cancer. In spite of more than 200 anticancer drugs presently approved for clinical use, none has been found to specifically and effectively inhibit cancer metastasis (Qian et al., 2017). Current diagnostic and treatment modalities to deal with this rising cancer burden worldwide are also inadequate and ineffective. Hence there is a mounting need to develop new therapeutic modalities to treat metastatic cancers. One approach is to prevent metastatic spread, which can be achieved by understanding the molecular and cellular mechanisms involved in malignancy and the aggressive spreading of the disease. In general, cancer cell metastasis comprises of an orderly sequence of pathological molecular events, collectively termed as metastatic cascade; starting with epithelial to mesenchymal transition (EMT) followed by extracellular matrix (ECM) remodeling; intravasation; survival of cancer cells in the blood stream; extravasation and colonization to prosper in a new compatible environment (Hegde et al., 2013). Future studies on different signaling pathways involved in these molecular events of metastatic cascade may provide novel therapeutic targets to develop new antimetastatic drugs against metastatic cancers.

The major risk factors associated with considerable deaths from cancer are: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, and alcohol use (Vineis and Wild, 2014). A remarkable amount of evidence from epidemiological, clinical

and laboratory research indicates the importance of diet and nutrition in cancer chemoprevention (Iqbal et al., 2017; Kaur et al., 2018; Mayne et al., 2016; World Cancer Research Fund and American Institute for Cancer Research, 2007). The World Cancer Research Fund and American Institute for Cancer Research (WCRF/AIRC) have released evidence based preventive recommendations including physical activity, avoidance of energy-dense foods, consumption of variety of fruits, vegetables, whole grains and pulses, and avoiding consumption of alcohol (World Cancer Research Fund and American Institute for Cancer Research, 2007). In last few decades, a large number of scientific efforts have been made to discover effective dietary phytochemicals for instance; phenolic acids, monophenols, polyphenols, complex carbohydrates for their use as chemopreventive agents (Surh, 2003; Weng and Yen, 2012). Among these, the ones generated by human gut microbiota from dietary phenolic compounds like condensed tannins, lignans and lignans have been found to be most useful (Högger, 2013). One of these bioactive phenolic metabolites is an Enterolactone (EL) which is a mammalian lignan derived from the dietary lignans. Several studies have revealed that EL possesses potent anti-cancer and/or protective properties against different cancers viz. breast, prostate, colo-rectal, lung, ovarian, endometrial, cervical cancers and hepatocellular carcinoma. The anti-cancer effects of EL have been mainly attributed to its anti-proliferative, pro-apoptotic, anti-inflammatory, anti-angiogenic and anti-metastatic activities. In this review, we provide a summarized account of the reported anti-cancer effects of EL at preclinical as well as clinical level.

2. Enterolactone: a mammalian lignan derived from dietary lignans

Plant lignans are large group of the PhE and regarded as an integral part of a healthy human diet (Adlercreutz, 2007). Dietary lignans are bioactive, non-caloric and phenolic compounds found in edible plants having structure similar to endogenous estrogen. Flax seeds and sesame seeds are the richest sources of lignans while other oil seeds, whole grain cereals, legumes, fruits, berries, vegetables, beverages and wine are also significant food sources (Fig. 1) of these dietary lignans (Peterson et al., 2010). Dietary lignans having significant health values include secoisolariciresinol (SECO), matairesinol (MAT), pinoresinol (PIN), medioresinol (MED), lariciresinol (LAR), syringaresinol (SYR), sesamin (SES, a lignan precursor), 7′- hydroxymatairesinol (HMR), arctigenin (ARC) and isolariciresinol (isoLAR) (Adlercreutz, 2007; Landete et al., 2016). These dietary lignans are metabolized to form nutritionally most significant enterolignans (also referred as mammalian lignans); enterodiol (ED) and enterolactone (EL) in various enzymatic steps including deglycosylation, demethylation, dehydroxylation, reduction, and dehydrogenation (Clavel et al., 2006b). Different strains of genera are involved in the metabolic conversion of dietary lignans into the enterolignans, which include *Bacteroides, Clostridium, Eubacterium and Eggerthella lenta* (Högger, 2013). Since EL appears to be the prime circulating enterolignan, its serum levels and urinary excretion levels are used as biomarkers for food lignan intakes (Peterson et al., 2010).

3. Pharmacokinetics of dietary and enterolignans in humans

To evaluate the absorption, distribution, metabolism and excretion (ADME) properties of dietary and enterolignans several pharmacokinetic (PK) studies have been carried out using

lignan rich foods. However, very few studies have been carried out with isolated lignans in humans. Since flaxseeds and sesame seeds are the richest sources of dietary lignans, most of the PK studies have been carried out upon ingestion of secoisolariciresinol diglucoside (SDG) and sesamin (SES). Dietary lignans are present in edible plants both as aglycones (without sugars) and as glycosides (with sugars). Lignan glycosides after absorption in gastrointestinal tract (GIT), get metabolized in aglycones and subsequently to enterolignans. Flaxseed contains 0.05–0.2% SDG as a major glycoside lignan which is present in it as an oligomer of SDG molecules complexed with hydroxymethylglutaric acid (Setchell et al., 2014). Another rich source of lignans are the sesame seeds belonging to the oil seed crop, *Sesamum indicum* in which sesaminol triglucoside (STG) is the most abundant lignan glycoside and SES is present as a prime fat soluble lignan along with other lignans such as sesamolin, sesaminol, sesamolinol, PIN and HMR among which SES acts as one of the major precursors of mammalian lignans in sesame seeds (Liu et al., 2006; Majdalawieh et al., 2017; Pen et al., 2005). The SDG and STG glycoside lignans are considered to undergo hydrolysis in the large intestine after oral administration with subsequent deglycosylation of both in order to form SECO which is an aglycone lignan. Unabsorbed SECO undergoes microbial demethylation and dehydroxylation to produce the enterolignans; ED and EL respectively (Clavel et al., 2006a; Lampe et al., 2006; Roncaglia et al., 2011). Although available data suggests ambiguity about the metabolic pathway of SES in humans, EL is considered as the final product of the SES metabolism, which is independent of intermediates of the pathway (Pen et al., 2005; Tomimori et al., 2013). Besides SDG and SES, the aglycone dietary lignans like LAR, PIN, MAT and others are absorbed directly or converted finally to EL through intermediates. PIN is first metabolized to LAR, which is further converted to SECO, and then to ED and EL while MAT is directly converted to EL. Detection of both enterolignans and dietary lignans in human serum and urine indicates that both types of lignans are absorbed from the gut (Clavel et al., 2006a; Miles et al., 2017). A recent study in humans has shown that, following single-bolus oral administration of SDG, the SECO appeared rapidly in serum with peak concentrations reaching after 5–7 h independent of the dose ingested or the extent of purity of the extract while the peak serum ED and EL concentrations appeared at 19.2 ± 2.6 h and 26.7 ± 2.5 h, respectively (Setchell et al., 2014). These results are consistent with a previous study on 12 healthy young adults where enterolignans started to appear in plasma after 8–10 h after ingestion of the purified SDG (Kuijsten et al., 2005).

Once produced by intestinal bacteria, ED and EL are absorbed, conjugated in the gut epithelium or liver with sulfate or glucuronic acid, and excreted in the urine and bile. Since EL (~11.6 h) has a longer half-life than ED (~9 h), it constitutes the majority of enterolignans in circulation or in urine excretion (Kuijsten et al., 2005; Miles et al., 2017; Setchell et al., 2014). In order to get a better understanding of the oral absorption characteristics of SDG, SECO, ED & EL, a systematic evaluation of the intestinal permeation and conjugative metabolism was conducted using the polarized Caco-2 cell system in recent study. This study addressed the intestinal permeability of these lignans where authors suggested that SECO, ED and EL are able to undergo passive permeation and conjugative metabolism by the Caco-2 cells (Mukker et al., 2014). These findings are consistent with the previous in-vitro study involving three human colon epithelial cell lines

where authors reported that the enterolignans (ED and EL) permeate human colon epithelial cells wherein they are conjugated with glucuronic acid or to a lesser extent with sulfate. The authors suggested that phase II metabolism of EL and ED may take place during uptake in the colon and colon epithelial cells may be responsible for this metabolism (Jansen et al., 2005). Although the conjugates of enterolignans are excreted in urine and bile usually, those that are re-excreted in bile undergo enterohepatic recycling (Kuijsten et al., 2005). In urine, EL and ED are excreted primarily as monoglucuronides (95% and 85%, respectively), with small percentages being excreted as monosulfates (2–10%) and free aglycones (0.3–1%). (Adlercreutz et al., 1995). It is important to note that there are obvious determinants of serum EL concentration which include dietary intake of EL precursors, health of gut microbiota along with other determinants like dietary habits, demographic factors, constipation, smoking, low or high body mass index, age, sex, education, fat intake and use of antibiotics (Adlercreutz, 2007).

4. Clinical evidence of cancer chemopreventive effects of EL

About 30 epidemiological studies supporting a protective role of dietary intake of EL and its plasma/serum/urine concentrations in several cancers are identified and summarized in Table 1. Among these 19 breast cancer, 5 prostate cancer, 3 colorectal cancer, 1 gastric cancer and 1 lung cancer study reported on the protective or inverse association between EL and risk of respective cancers. Most of these are case control studies with retrospective design and few are cohort studies with prospective design. Epidemiological studies of breast cancer reported that higher dietary intake of EL precursors and higher blood concentrations of EL are associated with the reduced risk of breast cancer, decreased mortality rate and better survival particularly in postmenopausal breast cancer patients but with little ambiguity among the data in relation to the estrogen receptor status particularly in estrogen receptor α + , estrogen receptor $\alpha-$ and estrogen receptor $\beta+$ breast cancers. However, a few studies have reported none or limited association between EL concentration derived from dietary lignans in plasma, serum or urine and risk of breast cancer (den Tonkelaar et al., 2001; Horn-Ross et al., 2001; Hultén et al., 2002; Kilkkinen et al., 2004; Kyrø et al., 2017; Touillaud et al., 2006; Verheus et al., 2007; Ward et al., 2008; Xie et al., 2013; Zeleniuch-Jacquotte et al., 2004). Prostate cancer studies also supported the hypothesis that higher dietary intake of PhE and blood concentrations of EL are associated with the reduced risk of prostate cancer in men. There are also studies that report no protective association between EL and risk of prostate cancer (Eriksen et al., 2017; Stattin et al., 2004, 2002; Travis et al., 2009; Wallström et al., 2017). Epidemiological studies suggest that high dietary intake of EL resulting in increased plasma concentrations of EL might protect against the risk of colon cancer particularly in women (Johnsen et al., 2010; Ward et al., 2010). While one nested case control study did not support the hypothesis that high plasma ED or EL concentrations are associated with reduced risk of colorectal cancer (Kuijsten et al., 2008), a Korean epidemiological study on gastric cancer concluded that interaction between CRK gene and PhE (genistein, daidzein, equol and EL) modify gastric cancer risk. It was also reported that high dietary intake of PhE producing EL and ED are associated with a decrease in risk in lung cancer. One case control study did not support a protective role of circulating lignans (EL) against endometrial cancer in both pre-and postmenopausal women (Zeleniuch-Jacquotte et al.,

2006). However majority of the clinical evidence strongly support the protective role of EL in the risk of breast, prostate, colon, gastric and lung cancers and indicates EL as a potential anticancer nutrition molecule.

5. Pre-clinical evidence of anticancer effects of EL on different types of cancer

5.1. Evidence from studies of EL in animal models of cancer

About 12 in-vivo animal studies evaluating the anticancer potential of EL was performed by its direct administration (Table 2). These studies include human cancer cell xenografts as well as chemically induced carcinogenesis by 7, 12-Dimethylbenz(a) anthracene (DMBA) and (N-ethyl-N′-nitro-N nitroso-guanidine) ENNG, and knockout models of ovariectomized mice and rats. In these studies EL was administered via oral or subcutaneous (SC) routes and intra tumor injections. EL was reported to exert its anticancer potential in breast cancer by both estrogen dependent and independent mechanisms (Jungeström et al., 2007). Consistent anticancer effects observed in breast cancer studies included reduction in tumor volume and size, increase in apoptosis, decrease in both stroma and cancer cell derived vascular endothelial growth factor (VEGF), inhibition of estradiol (E2) induced growth and angiogenesis, decrease in in-vivo release of interleukin-1 beta (IL-1β) and increase in interleukin-1 receptor antagonist (IL-1Ra) levels (Jungeström et al., 2007; Lindahl et al., 2011; Saarinen et al., 2010). One study confirmed that EL reduced the growth and metastasis of solid AH109A hepatomas in rats (Miura et al., 2007). Other studies on uterine cancer and colon cancer reported that EL exerts chemopreventive effects in the rat ENNG-uterine carcinogenesis model while it inhibits cell proliferation and induces cell death in COLO 201 human colon cancer xenografts, respectively (Danbara et al., 2005; Katsuda et al., 2004). All these preclinical animal studies provide strong evidence in favor of the chemopreventive or anticancer potential of EL in breast, liver, uterine and colon cancers.

5.2. Evidence from mechanistic studies of EL on human cancer cell lines

So far 30 in-vitro cell culture studies have been identified reporting on the anticancer activities of EL on several human cancer cell lines (Table 3). These studies reported various cellular and molecular mechanisms of EL against novel therapeutic targets in different types of cancers. EL was found to exhibit a host of activities including chemopreventive, antiproliferative, apoptotic, antimetastatic, immunomodulatory, chemosensitizing and radiosensitizing in different human cancer cell lines such as breast cancer, prostate cancer, colon cancer, lung cancer, ovarian cancer, choriocarcinoma, osteosarcoma and monocytic leukemia cell lines. Reported mechanistic end points on different therapeutic targets of EL in different cancer cells have been shown in Fig. 2 while major signaling pathways modulated by EL, in breast cancer and lung cancer have particularly been shown in Fig. 3. In prostate cancer, it was reported that EL induced apoptosis in human prostate carcinoma LNCaP cells by inhibiting Akt signaling pathway (Chen et al., 2007) while in the case of lung cancer, EL altered FAK-Src signaling pathway to suppress migration and invasion of A549 and H460 human lung cancer cell lines (Chikara et al., 2017a). In our recent work we have shown that EL exerts its antimetastatic breast cancer activity by suppressing invasion, migration,

colonization in-vitro; via inhibition of uPA/Plasmin/MMPs mediated ECM remodeling and by reverting TGF-β induced EMT via modulation of ERK-NFκB-Snail signaling pathway in triple negative MDA-MB-231 human breast cancer cells (Mali et al., 2017, 2018). It is important to note that EL was reported to show estrogen receptor dependent as well as estrogen receptor independent mechanisms in different breast cancer cell lines (Bigdeli et al., 2016a; Brooks and Thompson, 2005; Chen and Thompson, 2003; Di et al., 2018; Mali et al., 2017, 2012, 2018; Pianjing et al., 2011). Collectively most of these in-vitro human cell culture studies provide strong evidence in support of strong anticancer and antimetastatic potential of EL in several cancers.

6. Conclusions

Due to the high incidence and mortality rates and lack of new therapeutic agents targeting novel therapeutic strategies, cancer imposes a great burden of disease and challenges worldwide not only to the care providers but also to scientists. As mentioned earlier, diet, nutrition and physical activity are some of the most important determinants of cancer risk in humans through their in-part contribution to obesity, which is considered as a known risk factor for many malignancies (Mayne et al., 2016). By advance in nutrition-based research, it is now well accepted fact that diet not only plays a fundamental role in cancer prevention, but also contributes to the reduced treatment associated complications and the patient's well-being (World Cancer Research Fund and American Institute for Cancer Research, 2007). One of the important categories of potential nutrients having chemopreventive action is dietary lignans and their metabolites (enterolignans). In this review, we focused on EL which is a prime, nutrition-derived, bioactive circulating metabolite of most of the dietary lignans and considered as having potential, nutritionally significant anticancer activity in several cancers of both men and women. Initial preclinical and clinical data based on several epidemiological studies supports the chemopreventive role of EL, particularly in hormonal cancers. Whereas, recent preclinical data based on mechanistic studies involving human cell cultures and xenografts revealed the therapeutic potential of EL not only in hormonal cancers but also in other types of cancer.

Several, but not all, epidemiologic studies report reduced risks of breast cancer, prostate cancer, colorectal cancer, lung cancer, endometrial cancer and gastric cancer associated with higher exposure to dietary lignans and their metabolites (enterolignans), expressed as either dietary intakes or as plasma, serum, or urinary EL concentrations. These clinical evidence strongly support the chemopreventive role of EL in respective cancers by considering its ability to play an important role in reducing the risk of developing the cancer, lowering cancer related mortality and better survival. However it is important to note that most of these studies were carried out on breast and prostate cancer and very few studies were conducted on other cancers, particularly in western and European populations. We did not find any intervention clinical trial of EL in cancer patients, however several flaxseed or SDG intervention clinical trials are reported particularly in breast cancer (Calado et al., 2018).

In the case of preclinical animal studies, we found that very few studies were carried out by direct administration of EL to the cancer animal models (summarized in this review) and many studies were carried out on flaxseed or sesame seed diet supplementation to evaluate

their anticancer potential (not included in this review). Most of these in-vivo studies of EL are based on human xenografts, particularly of breast, liver, uterine and colon cancers and provide a strong evidence to support the anticancer and antimetastatic potential of EL by considering its ability to inhibit tumor growth and angiogenesis, to lower tumor burden, to promote tumor cell apoptosis, and to reduce metastasis. On the other hand, the in-vitro studies based on different human cancer cell lines provide deep insights into novel molecular and cellular mechanisms of EL which are capable of interfering the steps of carcinogenesis and metastasis by inhibiting adhesion, invasion, migration, proliferation, ECM remodeling, EMT, etc. Thus several in-vitro studies also provide a strong evidence to support anticancer and antimetastatic potential of EL. In this comprehensive review on EL and its role in cancer we propose this molecule as a potential candidate for anti cancer drug discovery or dietary supplements and nutraceuticals.

7. Future perspectives

In order to establish the protective and therapeutic association of EL with breast, prostate and other cancers, there is strong need to conduct more epidemiological studies and intervention trials in different ethnic populations. Future studies with a new wave of technology, based on novel approaches like genome-wide association studies (GWAS), metabolomics and nutritional epigenetics will provide more scientific clinical evidence to support the anticancer and antimetastatic potential of the EL. Moreover, very few clinical studies of EL in Asian and other populations project a great opportunity to both clinicians and scientists to carry out research in this diet-cancer research field.

Acknowledgments

Source(s) of support

This work was supported by an institutional funding.

References

Aarestrup J, Kyro C, Knudsen KEB, Weiderpass E, Christensen J, Kristensen M, Würtz AML, Johnsen NF, Overvad K, Tjonneland A, Olsen A, 2013 Plasma enterolactone and incidence of endometrial cancer in a case-cohort study of Danish women. Br. J. Nutr 109, 2269–2275. 10.1017/S0007114512004424. [PubMed: 23114205]

Abarzua S, Serikawa T, Szewczyk M, Richter DU, Pieehulla B, Briese V, 2012 Antiproliferative activity of lignans against the breast carcinoma cell lines MCF 7 and BT 20. Arch. Gynecol. Obstet 285, 1145–1151. 10.1007/s00404-011-2120-6. [PubMed: 22037685]

Adlercreutz H, 2007 Lignans and human health. Crit. Rev. Clin. Lab. Sci 10.1080/10408360701612942.

Adlercreutz H, Heikkinen R, Woods M, Fotsis T, Dwyer JT, Goldin BR, Gorbach SL, 1982 Excretion of the lignans enterolactone and enterodiol and of equol in omnivorous and vegetarian postmenopausal women and in women with breast cancer. Lancet 320, 1295–1299. 10.1016/S0140-6736(82)91507-0.

Adlercreutz H, van der Wildt J, Kinzel J, Attalla H, Wähälä K, Mäkelä T, Hase T, Fotsis T, 1995 Lignan and isoflavonoid conjugates in human urine. J. Steroid Biochem. Mol. Biol 52, 97–103. 10.1016/0960-0760(94)00146-D. [PubMed: 7857879]

Adlercreutz H, Vickery LE, 1993 Inhibition of human aromatase by mammalian lignans and isoflavonoid phytoestrogens. J. Steroid Biochem. Mol. Biol 44, 147–153. [PubMed: 8382517]

Azrad M, Vollmer RT, Madden J, Dewhirst M, Polascik TJ, Snyder DC, Ruffin MT, Moul JW, Brenner DE, Demark-Wahnefried W, 2013 Flaxseed-derived enterolactone is inversely associated with tumor cell proliferation in men with localized prostate cancer. J. Med. Food 16, 357–360. 10.1089/jmf.2012.0159. [PubMed: 23566060]

Bigdeli B, Goliaei B, Masoudi-Khoram N, Jooyan N, Nikoofar A, Rouhani M, Haghparast A, Mamashli F, 2016a Enterolactone: a novel radiosensitizer for human breast cancer cell lines through impaired DNA repair and increased apoptosis. Toxicol. Appl. Pharmacol 313, 180–194. 10.1016/j.taap.2016.10.021. [PubMed: 27984132]

Bigdeli B, Goliaei B, Masoudi-Khoram N, Jooyan N, Nikoofar A, Rouhani M, Haghparast A, Mamashli F, 2016b Enterolactone: a novel radiosensitizer for human breast cancer cell lines through impaired DNA repair and increased apoptosis. Toxicol. Appl. Pharmacol 313, 180–194. 10.1016/j.taap.2016.10.021. [PubMed: 27984132]

Boccardo F, Lunardi G, Guglielmini P, Parodi M, Murialdo R, Schettini G, Rubagotti A, 2004 Serum enterolactone levels and the risk of breast cancer in women with palpable cysts. Eur. J. Cancer 40, 84–89. 10.1016/S0959-8049(03)00576-8. [PubMed: 14687793]

Bommareddy A, Zhang XY, Kaushik RS, Dwivedi C, 2010 Effects of components present in flaxseed on human colon adenocarcinoma Caco-2 cells: possible mechanisms of flaxseed on colon cancer development in animals. Drug Discov. Ther. 4, 184–189. [PubMed: 22491182]

Brooks JD, Thompson LU, 2005 Mammalian lignans and genistein decrease the activities of aromatase and 17βhydroxysteroid dehydrogenase in MCF-7 cells. J. Steroid Biochem. Mol. Biol 94, 461–467. 10.1016/j.jsbmb.2005.02.002. [PubMed: 15876411]

Buck K, Vrieling A, Zaineddin AK, Becker S, Hušing A, Kaaks R, Linseisen J, Fleseh-Janys D, Chang-Claude J, 2011a Serum enterolactone and prognosis of postmenopausal breast cancer. J. Clin. Oncol 29, 3730–3738. 10.1200/JCO.2011.34.6478. [PubMed: 21900115]

Buck K, Zaineddin AK, Vrieling A, Heinz J, Linseisen J, Fleseh-Janys D, Chang-Claude J, 2011b Estimated enterolignans, lignan-rich foods, and fibre in relation to survival after postmenopausal breast cancer. Br. J. Cancer 105, 1151–1157. 10.1038/bjc.2011.374. [PubMed: 21915130]

Buck K, Zaineddin AK, Vrieling A, Linseisen J, Chang-Claude J, 2010 Meta-analyses of lignans and enterolignans in relation to breast cancer risk. Am. J. Clin. Nutr 92, 141–153. 10.3945/ajcn.2009.28573. [PubMed: 20463043]

Calado A, Neves PM, Santos T, Ravasco P, 2018 The effect of flaxseed in breast cancer: a literature review. Front. Nutr 5, 4 10.3389/fnut.2018.00004. [PubMed: 29468163]

Chen J, Thompson LU, 2003 Lignans and tamoxifen, alone or in combination, reduce human breast cancer cell adhesion, invasion and migration in vitro. Breast Cancer Res. Treat 80, 163–170. 10.1023/a:1024513815374. [PubMed: 12908819]

Chen L-H, Fang J, Li H, Demark-Wahnefried W, Lin X, 2007 Enterolactone induces apoptosis in human prostate carcinoma LNCaP cells via a mitochondrial-mediated, caspase-dependent pathway. Mol. Cancer Ther 6, 2581–2590. 10.1158/1535-7163.MCT-07-0220. [PubMed: 17876055]

Chen L, Fang J, Sun Z, Li H, Wu Y, Demark-wahnefried W, Lin X, 2009 Enterolactone inhibits insulin-like growth factor-1 receptor signaling in human prostatic carcinoma PC-3 cells. J. Nutr 139, 653–659. 10.3945/jn.108.101832. [PubMed: 19211828]

Chikara S, Lindsey K, Borowicz P, Christofidou-Solomidou M, Reindl KM, 2017a Enterolactone alters FAK-Src signaling and suppresses migration and invasion of lung cancer cell lines. BMC Complement. Altern. Med 17, 30 10.1186/s12906-016-1512-3. [PubMed: 28068967]

Chikara S, Lindsey K, Dhillon H, Mamidi S, Kittilson J, Christofidou-Solomidou M, Reindl KM, 2017b Enterolactone Induces G1-phase cell cycle arrest in nonsmall cell lung cancer cells by downregulating cyclins and cyclin-dependent kinases. Nutr. Cancer 69, 652–662. 10.1080/01635581.2017.1296169. [PubMed: 28323486]

Clavel T, Doré J, Blaut M, 2006a Bioavailability of lignans in human subjects. Nutr. Res. Rev 19, 187–196. 10.1017/S0954422407249704. [PubMed: 19079885]

Clavel T, Henderson G, Engst W, Doré J, Blaut M, 2006b Phylogeny of human intestinal bacteria that activate the dietary lignan secoisolariciresinol diglucoside. FEMS Microbiol. Ecol 55, 471–478. 10.1111/j.1574-6941.2005.00057.x. [PubMed: 16466386]

Corsini E, Dell'Agli M, Facchi A, De Fabiani E, Lucchi L, Boraso MS, Marinovich M, Galli CL, 2010 Enterodiol and enterolactone modulate the immune response by acting on nuclear factor-κB (NF-κB) signaling. J. Agric. Food Chem 58, 6678–6684. 10.1021/jf100471n. [PubMed: 20446732]

Dai Q, Franke AA, Jin F, Shu X-O, Hebert JR, Custer LJ, Cheng J, Gao Y-T, Zheng W, 2002 Urinary excretion of phytoestrogens and risk of breast cancer among Chinese women in Shanghai. Cancer Epidemiol. Biomark. Prev 11, 815–821.

Dale IL, Gant TW, Chipman JK, Kerr DJ, 1998 Regulation of c- fos transcription by chemopreventive isoflavonoids and lignans in MDA-MB-468 breast cancer cells. Eur. J. Cancer 34, 1425–1431. [PubMed: 9849427]

Danbara N, Yuri T, Tsujita-Kyutoku M, Tsukamoto R, Uehara N, Tsubura A, 2005 Enterolactone induces apoptosis and inhibits growth of colo 201 human colon cancer cells both in vitro and in vivo. Anticancer Res. 25, 2269–2276. [PubMed: 16158974]

den Tonkelaar I, Keinan-Boker L, Veer PV, Arts CJ, Adlercreutz H, Thijssen JH, Peeters PH, 2001 Urinary phytoestrogens and postmenopausal breast cancer risk. Cancer Epidemiol. Biomark. Prev 10, 223–228.

Di Y, De Silva F, Krol ES, Alcorn J, 2018 Flaxseed lignans enhance the cytotoxicity of chemotherapeutic agents against breast cancer cell lines MDA-MB-231 and SKBR3. Nutr. Cancer 5581, 1–10. 10.1080/01635581.2018.1421677.

Eriksen AK, Kyrø C, Nørskov N, Bolvig AK, Christensen J, Tjønneland A, Overvad K, Landberg R, Olsen A, 2017 Prediagnostic enterolactone concentrations and mortality among Danish men diagnosed with prostate cancer. Eur. J. Clin. Nutr 71, 1235–1240. 10.1038/ejcn.2017.42. [PubMed: 28378849]

Ervik M, Lam F, Ferlay J, Mery L, Soerjomataram I, Bray F, 2016 Cancer Today. International Agency for Research on Cancer, Lyon, France.

Feng J, Shi Z, Ye Z, 2008 Effects of metabolites of the lignans enterolactone and enterodiol on osteoblastic differentiation of MG-63 cells. Biol. Pharm. Bull 31, 1067–1070. 10.1248/bpb.31.1067. [PubMed: 18520031]

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F, 2015 Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer 136, E359–E386. 10.1002/ijc.29210. [PubMed: 25220842]

GarÍfa-mateos D, GarÍfa-villalba R, Angel J, Carlos J, Merino G, Álvarez AI, 2017 The Breast Cancer Resistance Protein (BCRP / ABCG2) influences the levels of enterolignans and their metabolites in plasma, milk and mammary gland. J. Funct. Foods J 35, 648–654. 10.1016/j.jff.2017.06.038.

Global Burden of Disease Cancer Collaboration, 2017 Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015. JAMA Oncol. 3, 524 10.1001/jamaoncol.2016.5688. [PubMed: 27918777]

Guglielmini P, Rubagotti A, Boccardo F, 2012 Serum enterolactone levels and mortality outcome in women with early breast cancer: a retrospective cohort study. Breast Cancer Res. Treat 132, 661–668. 10.1007/s10549-011-1881-8. [PubMed: 22094938]

He J, Wang S, Zhou M, Yu W, Zhang Y, He X, 2015 Phytoestrogens and risk of prostate cancer: a meta-analysis of observational studies. World J. Surg. Oncol 13 10.1186/s12957-015-0648-9.

Heald CL, Ritchie MR, Bolton-Smith C, Morton MS, Alexander FE, 2007 Phytooestrogens and risk of prostate cancer in Scottish men. Br. J. Nutr 98, 388–396. 10.1017/S0007114507700703. [PubMed: 17403269]

Hedelin M, Klint Å, Chang ET, Bellocco R, Johansson JE, Andersson SO, Heinonen SM, Adlercreutz H, Adami HO, Grönberg H, Bälter KA, 2006 Dietary phytoestrogen, serum enterolactone and risk of prostate cancer: the Cancer Prostate Sweden Study (Sweden). Cancer Causes Control 17, 169–180. 10.1007/s10552-005-0342-2. [PubMed: 16425095]

Hegde MV, Mali AV, Chandorkar SS, 2013 What is a cancer cell? Why does it metastasize? Asian Pac. J. Cancer Prev 14, 3987–3989. 10.7314/APJCP.2013.14.6.3987. [PubMed: 23886219]

Ho CKM, Halley L, Wei J, Habib FK, 2012 Analysis of prostate cancer association with four single-nucleotide polymorphisms from genome-wide studies and serum phytoestrogen concentrations. Prostate Cancer Prostatic Dis. 15, 365–368. 10.1038/pcan.2012.24. [PubMed: 22733159]

Högger P, 2013 Nutrition-derived bioactive metabolites produced by gut microbiota and their potential impact on human health. Nutr. Med 1, 1–32.

Horn-Ross PL, John EM, Lee M, Stewart SL, Koo J, Sakoda LC, Shiau AC, Goldstein J, Davis P, Perez-Stable EJ, 2001 Phytoestrogen consumption and breast cancer risk in a multiethnic population: the Bay Area Breast Cancer Study. Am. J. Epidemiol 154, 434–441. 10.1093/AJE/154.5.434. [PubMed: 11532785]

Hultén K, Winkvist A, Lenner P, Johansson R, Adlercreutz H, Hallmans G, 2002 An incident case-referent study on plasma enterolactone and breast cancer risk. Eur. J. Nutr 41, 168–176. 10.1007/s00394-002-0373-3. [PubMed: 12242585]

Ilbeigi D, Nourbakhsh M, Khaghani S, Einollahi N, Kheiripour N, Gholinejad Z, Alaee M, Saberian M, 2017 Enterolactone reduces telomerase activity and the level of its catalytic subunit in breast cancer cells. Cell J. 19, 37–43. 10.22074/cellj.2017.4705. [PubMed: 28580306]

Ingram D, Sanders K, Kolybaba M, Lopez D, 1997 Case-control study of phytoestrogens and breast cancer. Lancet 350, 990–994. 10.1016/S0140-6736(97)01339-1. [PubMed: 9329514]

Iqbal J, Abbasi BA, Mahmood T, Kanwal S, Ali B, Shah SA, Khalil AT, 2017 Plant-derived anticancer agents: a green anticancer approach. Asian Pac. J. Trop. Biomed 7, 1129–1150. 10.1016/j.apjtb.2017.10.016.

Jansen GHE, Arts ICW, Nielen MWF, Müller M, Hollman PCH, Keijer J, 2005 Uptake and metabolism of enterolactone and enterodiol by human colon epithelial cells. Arch. Biochem. Biophys 435, 74–82. 10.1016/j.abb.2004.12.015. [PubMed: 15680909]

Johnsen NF, Olsen A, Thomsen BLR, Christensen J, Egeberg R, Bach Knudsen KE, Loft S, Overvad K, Tjønneland A, 2010 Plasma enterolactone and risk of colon and rectal cancer in a case-cohort study of Danish men and women. Cancer Causes Control 21, 153–162. 10.1007/s10552-009-9445-5. [PubMed: 19844797]

Jungeström MB, Thompson LU, Dabrosin C, 2007 Flaxseed and its lignans inhibit estradiol-induced growth, angiogenesis, and secretion of vascular endothelial growth factor in human breast cancer xenografts in vivo. Clin. Cancer Res 13, 1061–1067. 10.1158/1078-0432.CCR-06-1651. [PubMed: 17289903]

Katsuda S, Yoshida M, Saarinen N, Smeds A, Nakae D, Santti R, Maekawa A, 2004 Chemopreventive effects of hydroxymatairesinol on uterine carcinogenesis in Donryu rats. Exp. Biol. Med 229, 417–424.

Kaur V, Kumar M, Kumar A, Kaur K, Singh V, Kaur S, 2018 Pharmacotherapeutic potential of phytochemicals: implications in cancer chemoprevention and future perspectives. Biomed. Pharmacother 97, 564–586. [PubMed: 29101800]

Kilkkinen A, Virtamo J, Vartiainen E, Sankila R, Virtanen MJ, Adlercreutz H, Pietinen P, 2004 Serum enterolactone concentration is not associated with breast cancer risk in a nested case-control study. Int. J. Cancer 108, 277–280. 10.1002/ijc.11519. [PubMed: 14639615]

Kuijsten A, Arts ICW, Hollman PCH, Van't Veer P, Kampman E, 2006 Plasma enterolignans are associated with lower colorectal adenoma risk. Cancer Epidemiol. Biomark. Prev 15, 1132–1136. 10.1158/1055-9965.EPI-05-0991.

Kuijsten A, Arts ICW, Vree TB, Hollman PCH, 2005 Pharmacokinetics of enterolignans in healthy men and women consuming a single dose of secoisolariciresinol diglucoside. J. Nutr 135, 795–801. [PubMed: 15795437]

Kuijsten A, Hollman PCH, Boshuizen HC, Buijsman MNCP, Van't Veer P, Kok FJ, Arts ICW, Bueno-De-Mesquita HB, 2008 Plasma enterolignan concentrations and colorectal cancer risk in a nested case-control study. Am. J. Epidemiol 167, 734–742 . 10.1093/aje/kwm349. [PubMed: 18192676]

Kyrø C, Hansen L, Frederiksen K, Nørskov NP, Bach Knudsen KE, Eriksen AK, Holm M, Tjønneland A, Olsen A, 2017 Pre-diagnostic plasma enterolactone concentrations and breast cancer prognosis among postmenopausal women - The Danish diet, cancer and health cohort. Clin. Nutr 1–9. 10.1016/j.clnu.2017.10.023. [PubMed: 28935438]

Lampe JW, Atkinson C, Hullar MAJ, 2006 Assessing exposure to lignans and their metabolites in humans. J. AOAC Int 89, 1174–1181. [PubMed: 16915861]

Landete JM, Arqués J, Medina M, Gaya P, de Las Rivas BD, Muñoz R, 2016 Bioactivation of phytoestrogens: intestinal bacteria and health. Crit. Rev. Food Sci. Nutr 56, 1826–1843. 10.1080/10408398.2013.789823. [PubMed: 25848676]

Lin X, Switzer BR, Demark-Wahnefried W, 2001 Effect of mammalian lignans on the growth of prostate cancer cell lines. Anticancer Res.

Lindahl G, Saarinen N, Abrahamsson A, Dabrosin C, 2011 Tamoxifen, flaxseed, and the lignan enterolactone increase stroma- and cancer cell-derived IL-1Ra and decrease tumor angiogenesis in estrogen-dependent breast cancer. Cancer Res. 71, 51–60. 10.1158/0008-5472.CAN-10-2289. [PubMed: 21097717]

Linseisen J, Piller R, Hermann S, Chang-Claude J, 2004 Dietary phytoestrogen intake and premenopausal breast cancer risk in a German case-control study. Int. J. Cancer 110, 284–290. 10.1002/ijc.20119. [PubMed: 15069695]

Liu H, Liu J, Wang S, Zeng Z, Li T, Liu Y, Mastriani E, Li QH, Bao HX, Zhou YJ, Wang X, Hu S, Gao S, Qi Y, Shen Z, Wang H, Yu M, Gao T, Johnston RN, Liu SL, 2017 Enterolactone has stronger effects than enterodiol on ovarian cancer. J. Ovarian Res 10, 49 10.1186/s13048-017-0346-z. [PubMed: 28738876]

Liu Z, Saarinen NM, Thompson LU, 2006 Sesamin is one of the major precursors of mammalian lignans in sesame seed (Sesamum indicum) as observed in vitro and in rats. J. Nutr 136, 906–912 (https://doi.org/136/4/906)(pii). [PubMed: 16549449]

Mabrok HB, Klopfleisch R, Ghanem KZ, Clavel T, Blaut M, Loh G, 2012 Lignan transformation by gut bacteria lowers tumor burden in a gnotobiotic rat model of breast cancer. Carcinogenesis 33, 203–208. 10.1093/carcin/bgr256. [PubMed: 22080573]

Majdalawieh AF, Massri M, Nasrallah GK, 2017 A comprehensive review on the anti-cancer properties and mechanisms of action of sesamin, a lignan in sesame seeds (Sesamum indicum). Eur. J. Pharmacol 10.1016/j.ejphar.2017.10.020.

Mali AV, Joshi AA, Hegde MV, Kadam SS, 2017 Enterolactone suppresses proliferation, migration and metastasis of MDA-MB-231 breast cancer cells through inhibition of uPA induced plasmin activation and MMPs-mediated ECM remodeling. Asian Pac. J. Cancer Prev 18, 905–915. 10.22034/APJCP.2017.18.4.905. [PubMed: 28545187]

Mali AV, Wagh UV, Chandorkar SS, Patole MV, Hegde MV, Surve SV, 2012 In vitro anti-metastatic activity of enterolactone, a mammalian lignan derived from flax lignan, and down-regulation of matrix metalloproteinases in MCF-7 and MDA MB 231 cell lines. Indian J. Cancer 49, 181 10.4103/0019-509X.98948. [PubMed: 22842186]

Mali AV, Joshi AA, Hegde MV, Kadam SS, 2018 Enterolactone modulates the ERK/NF-κB/Snail signaling pathway in triple-negative breast cancer cell line MDA-MB- 231 to revert the TGF-β-induced epithelial–mesenchymal transition. Cancer Biol. Med 15, 137–156. 10.20892/j.issn.2095-3941.2018.0012. [PubMed: 29951338]

Mayne ST, Playdon MC, Rock CL, 2016 Diet, nutrition, and cancer: past, present and future. Nat. Rev. Clin. Oncol 13, 504–515. 10.1038/nrclinonc.2016.24. [PubMed: 26951041]

McCann MJ, Gill CIR, Linton T, Berrar D, McGlynn H, Rowland IR, 2008 Enterolactone restricts the proliferation of the LNCaP human prostate cancer cell linein vitro. Mol. Nutr. Food Res 52, 567–580. 10.1002/mnfr.200700052. [PubMed: 18398867]

Mccann MJ, Rowland IR, Roy NC, 2013 Anti-proliferative effects of physiological concentrations of enterolactone in models of prostate tumourigenesis. Mol. Nutr. Food Res 57, 212–224. 10.1002/mnfr.201200362. [PubMed: 23148045]

McCann MJ, Rowland IR, Roy NC, 2014 The anti-proliferative effects of enterolactone in prostate cancer cells: evidence for the role of DNA licencing genes, Mi-R106b cluster expression, And PTEN dosage. Nutrients 6, 4839–4855. 10.3390/nu6114839. [PubMed: 25372501]

McCann SE, Moysich KB, Freudenheim JL, Ambrosone CB, Shields PG, 2002 The risk of breast cancer associated with dietary lignans differs by CYP17 genotype in women. J. Nutr 132, 3036–3041. [PubMed: 12368392]

McCann SE, Muti P, Vito D, Edge SB, Trevisan M, Freudenheim JL, 2004 Dietary lignan intakes and risk of pre- and postmenopausal breast cancer. Int. J. Cancer 111, 440–443. 10.1002/ijc.20262. [PubMed: 15221974]

Miles FL, Navarro SL, Schwarz Y, Gu H, Djukovic D, Randolph TW, Shojaie A, Kratz M, Hullar MAJ, Lampe PD, Neuhouser ML, Raftery D, Lampe JW, 2017 Plasma metabolite abundances are associated with urinary enterolactone excretion in healthy participants on controlled diets. Food Funct. 8, 3209–3218. 10.1039/C7FO00684E. [PubMed: 28808723]

Miura D, Saarinen NM, Miura Y, Santti R, Yagasaki K, 2007 Hydroxymatairesinol and its mammalian metabolite enterolactone reduce the growth and metastasis of subcutaneous AH109A hepatomas in rats. Nutr. Cancer 58, 49–59. 10.1080/01635580701308133. [PubMed: 17571967]

Mukker JK, Michel D, Muir AD, Krol ES, Alcorn J, 2014 Permeability and conjugative metabolism of flaxseed lignans by caco-2 human intestinal cells. J. Nat. Prod 77, 29–34. 10.1021/np4004905. [PubMed: 24417583]

Olsen A, Christensen J, Knudsen KEB, Johnsen NF, Overvad K, Tjønneland A, 2011 Prediagnostic plasma enterolactone levels and mortality among women with breast cancer. Breast Cancer Res. Treat 128, 883–889. 10.1007/s10549-011-1397-2. [PubMed: 21340481]

Olsen A, Erik K, Knudsen B, Thomsen BL, Loft S, Stripp C, Overvad K, Møller S, Tjønneland A, 2004 plasma enterolactone and breast cancer incidence by estrogen receptor status plasma enterolactone and breast cancer incidence by estrogen receptor status. Cancer Epidemiol. Biomark. Prev 13, 2084–2089.

Pen L, Heinonen S, Aura A, Adlercreutz H, 2005 Dietary Sesamin Is converted to enterolactone in humans. J. Nutr 135, 1056–1062 (https://doi.org/135/5/1056) (pii). [PubMed: 15867281]

Peterson J, Dwyer J, Adlercreutz H, Scalbert A, Jacques P, McCullough ML, 2010 Dietary lignans: physiology and potential for cardiovascular disease risk reduction. Nutr. Rev 68, 571–603. 10.1111/j.1753-4887.2010.00319.x. [PubMed: 20883417]

Pianjing P, Thiantanawat A, Rangkadilok N, Watcharasit P, Mahidol C, Satayavivad J, 2011 Estrogenic activities of sesame lignans and their metabolites on human breast cancer cells. J. Agric. Food Chem 59, 212–221. 10.1021/jf102006w. [PubMed: 21141889]

Pietinen P, Stumpf K, Männistö S, Kataja V, Uusitupa M, Adlercreutz H, 2001 Serum enterolactone and risk of breast cancer: a case-control study in eastern Finland. Cancer Epidemiol. Biomark. Prev 10, 339–344.

Piller R, Chang-Claude J, Linseisen J, 2006 Plasma enterolactone and genistein and the risk of premenopausal breast cancer. Eur. J. Cancer Prev 15, 225–232. 10.1097/01.cej.0000197449.56862.75. [PubMed: 16679865]

Power KA, Saarinen NM, Chen JM, Thompson LU, 2006a Mammalian lignans enterolactone and enterodiol, alone and in combination with the isoflavone genistein, do not promote the growth of MCF-7 xenografts in ovariectomized athymic nude mice. Int. J. Cancer 118, 1316–1320. 10.1002/ijc.21464. [PubMed: 16152607]

Power KA, Ward WE, Chen JM, Saarinen NM, Thompson LU, 2006b Genistein alone and in combination with the mammalian lignans enterolactone and enterodiol induce estrogenic effects on bone and uterus in a postmenopausal breast cancer mouse model. Bone 39, 117–124. 10.1016/j.bone.2005.12.015. [PubMed: 16469549]

Qian C-N, Mei Y, Zhang J, 2017 Cancer metastasis: issues and challenges. Chin. J. Cancer 36, 38 10.1186/s40880-017-0206-7. [PubMed: 28372569]

Qu H, Madl RL, Takemoto DJ, Baybutt RC, Wang W, 2005 Lignans are involved in the antitumor activity of wheat bran in colon cancer SW480 cells. J. Nutr 135, 598–602. [PubMed: 15735100]

Roncaglia L, Amaretti A, Raimondi S, Leonardi A, Rossi M, 2011 Role of bifidobacteria in the activation of the lignan secoisolariciresinol diglucoside. Appl. Microbiol. Biotechnol 92, 159–168. 10.1007/s00253-011-3338-8. [PubMed: 21614502]

Saarinen NM, Abrahamsson A, Dabrosin C, 2010 Estrogen-induced angiogenic factors derived from stromal and cancer cells are differently regulated by enterolactone and genistein in human breast cancer in vivo. Int. J. Cancer 127, 737–745. 10.1002/ijc.25052. [PubMed: 19924815]

Saarinen NM, Huovinen R, Warri A, Makela SI, Valentin-Blasini L, Sjoholm R, Ammala J, Lehtila R, Eckerman C, Collan YU, Santti RS, 2002 Enterolactone inhibits the growth of 7,12-Dimethylbenz(a) anthracene-induced mammary carcinomas in the rat. Mol. Cancer Ther 1, 869–876. [PubMed: 12492120]

Sehabath M, Hernandez L, Pillow P, Wu X, Spitz M, 2005 Dietary phytoestrogens and lung cancer risk. JAMA 294, 1493–1504. 10.1016/S0169-5002(05)80187-4. [PubMed: 16189362]

Schröder L, Richter DU, Pieehulla B, Chrobak M, Kuhn C, Schulze S, Abarzua S, Jeschke U, Weissenbacher T, 2016 Effects of phytoestrogen extracts isolated from elder flower on hormone production and receptor expression of trophoblast tumor cells JEG-3 and BeWo, as well as MCF7 breast cancer cells. Nutrients 8, 616 10.3390/nu8100616.

Seibold P, Vrieling A, Johnson TS, Buck K, Behrens S, Kaaks R, Linseisen J, Obi N, Heinz J, Fleseh-Janys D, Chang-Claude J, 2014 Enterolactone concentrations and prognosis after postmenopausal breast cancer: assessment of effect modification and meta-analysis. Int. J. Cancer 135, 923–933. 10.1002/ijc.28729. [PubMed: 24436155]

Setchell KDR, Brown NM, Zimmer-Nechemias L, Wolfe B, Jha P, Heubi JE, 2014 Metabolism of secoisolariciresinol-diglycoside the dietary precursor to the intestinally derived lignan enterolactone in humans. Food Funct. 5, 491–501. 10.1039/c3fo60402k. [PubMed: 24429845]

Sonestedt E, Borgquist S, Ericson U, Gullberg B, Olsson H, Adlercreutz H, Goran L, Wirfalt E, 2008 Enterolactone is differently associated with estrogen receptor B – negative and – positive breast cancer in a Swedish Nested Case-Control Study. Cancer Epidemiol. Biomark. Prev 17, 3241–3252. 10.1158/1055-9965.EPI-08-0393.

Stattin P, Adlercreutz H, Tenkanen L, Jellum E, Lumme S, Hallmans G, Harvei S, Teppo L, Stumpf K, Luostarinen T, Lehtinen M, Dillner J, Hakama M, 2002 Circulating enterolactone and prostate cancer risk: a nordic nested case-control study. Int. J. Cancer 99, 124–129. 10.1002/ijc.10313. [PubMed: 11948503]

Stattin P, Bylund A, Biessy C, Kaaks R, Hallmans G, Adlercreutz H, 2004 Prospective study of plasma enterolactone and prostate cancer risk (Sweden). Cancer Causes Control 15, 1095–1102. [PubMed: 15801493]

Stewart BW, Bray F, Forman D, Ohgaki H, Straif K, Ullrich A, Wild CP, 2016 Cancer prevention as part of precision medicine: “plenty to be done.”. Carcinogenesis 37, 2–9. 10.1093/carcin/bgv166. [PubMed: 26590901]

Sung MK, Lautens M, Thompson LU, 1998 Mammalian lignans inhibit the growth of estrogen-independent human colon tumor cells. Anticancer Res. 18, 1405–1408. [PubMed: 9673348]

Surh Y-J, 2003 Cancer chemoprevention with dietary phytochemicals. Nat. Rev. Cancer 3, 768–780. 10.1038/nrc1189. [PubMed: 14570043]

Tomimori N, Tanaka Y, Kitagawa Y, Fujii W, Sakakibara Y, Shibata H, 2013 Pharmacokinetics and safety of the sesame lignans, sesamin and episesamin, in healthy subjects. Biopharm. Drug Dispos 34, 462–473. 10.1002/bdd.1862. [PubMed: 24014208]

Touillaud MS, Thiebaut ACM, Fournier A, Niravong M, Boutron-Ruault M-C, Clavel-Chapelon F, 2007 Dietary lignan intake and postmenopausal breast cancer risk by estrogen and progesterone receptor status. J. Natl. Cancer Inst 99, 475–486. 10.1093/jnci/djk096. [PubMed: 17374837]

Touillaud MS, Thiebaut ACM, Niravong M, Boutron-Ruault M-C, Clavel-Chapelon F, 2006 No association between dietary phytoestrogens and risk of premenopausal breast cancer in a French Cohort Study. Cancer Epidemiol. Biomark. Prev 15, 2574–2576. 10.1158/1055-9965.EPI-06-0543.

Travis RC, Spencer EA, Allen NE, Appleby PN, Roddam AW, Overvad K, Johnsen NF, Olsen A, Kaaks R, Linseisen J, Boeing H, Nöthlings U, Bueno-De-Mesquita HB, Ros MM, Sacerdote C, Palli D, Tumino R, Berrino F, Trichopoulou A, Dilis V, Trichopoulos D, Chirlaque MD, Ardanaz E, Larranaga N, Gonzalez C, Suárez LR, Sánchez MJ, Bingham S, Khaw KT, Hallmans G, Stattin P, Rinaldi S, Slimani N, Jenab M, Riboli E, Key TJ, 2009 Plasma phytooestrogens and prostate cancer in the European prospective investigation into cancer and nutrition. Br. J. Cancer 100, 1817–1823. 10.1038/sj.bjc.6605073. [PubMed: 19436304]

Verheus M, Van Gils CH, Keinan-Boker L, Grace PB, Bingham SA, Peeters PHM, 2007 Plasma phytoestrogens and subsequent breast cancer risk. J. Clin. Oncol 25, 648–655. 10.1200/JCO.2006.06.0244. [PubMed: 17200150]

Vineis P, Wild CP, 2014 Global cancer patterns: causes and prevention. Lancet 383, 549–557. 10.1016/S0140-6736(13)62224-2. [PubMed: 24351322]

Wallström P, Drake I, Sonestedt E, Gullberg B, Bjartell A, Olsson H, Adlercreutz H, Tikkanen MJ, Wirfält E, 2017 Plasma enterolactone and risk of prostate cancer in middle-aged Swedish men. Eur. J. Nutr 1–12. 10.1007/s00394-017-1530-z.

Wang W, Liu LQ, Higuchi CM, Chen H, 1998 Induction of NADPH: quinone reductase by dietary phytoestrogens in colonic Colo205 cells. Biochem. Pharmacol 56, 189–195. 10.1016/S0006-2952(98)00141-5. [PubMed: 9698072]

Ward H.a., Kuhnle GGC, Mulligan A.a., Lentjes M.a.H., Luben RN, Khaw K, 2010 Breast, colorectal, and prostate cancer risk in the European prospective investigation into cancer and nutrition – Norfolk in relation to phytoestrogen intake derived from an improved database 1 – 4. Am. J. Clin. Nutr 91, 440–448. 10.3945/ajcn.2009.28282.1. [PubMed: 20007303]

Ward H, Chapelais G, Kuhnle GGC, Luben R, Khaw KT, Bingham S, 2008 Breast cancer risk in relation to urinary and serum biomarkers of phytoestrogen exposure in the European prospective into cancer-Norfolk cohort study. Breast Cancer Res. 10, 1–9. 10.1186/bcr1995.

Weng CJ, Yen GC, 2012 Chemopreventive effects of dietary phytochemicals against cancer invasion and metastasis: phenolic acids, monophenol, polyphenol, and their derivatives. Cancer Treat. Rev 38, 76–87. 10.1016/j.ctrv.2011.03.001. [PubMed: 21481535]

World Cancer Research Fund, American Institute for Cancer Research, 2007 Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Cancer Res (https://doi.org/978-0-9722522-2-5).

Xie J, Tworoger SS, Franke AA, Terry KL, Rice MS, Rosner BA, Willett WC, Hankinson SE, Eliassen AH, 2013 Plasma enterolactone and breast cancer risk in the Nurses' Health Study II. Breast Cancer Res. Treat 139, 801–809. 10.1007/s10549-013-2586-y. [PubMed: 23760859]

Xiong X-Y, Hu X-J, Li Y, Liu C-M, 2015 Inhibitory effects of enterolactone on growth and metastasis in human breast cancer. Nutr. Cancer 67,1326–1334. 10.1080/01635581.2015.1082113.

Yang JJ, Cho LY, Ko KP, Shin A, Ma SH, Choi BY, Han DS, Song KS, Kim YS, Lee JY, Han BG, Chang SH, Shin HR, Kang D, Yoo KY, Park SK, 2012 Genetic susceptibility on cagA-interacting molecules and gene-environment interaction with phytoestrogens: a putative risk factor for gastric cancer. PLoS One 7, e31020 10.1371/journal.pone.0031020. [PubMed: 22383989]

Zaineddin AK, Vrieling A, Buck K, Becker S, Linseisen J, Fleseh-Janys D, Kaaks R, Chang-Claude J, 2012 Serum enterolactone and postmenopausal breast cancer risk by estrogen, progesterone and herceptin 2 receptor status. Int. J. Cancer 130, 1401–1410. 10.1002/ijc.26157. [PubMed: 21544804]

Zeleniueh-Jaequotte A, Adlercreutz H, Shore RE, Koenig KL, Kato I, Arslan AA, Toniolo P, 2004 Circulating enterolactone and risk of breast cancer: a prospective study in New York. Br. J. Cancer 91, 99–105. 10.1038/sj.bjc.6601893. [PubMed: 15226762]

Zeleniueh-Jaequotte A, Lundin E, Micheli A, Koenig KL, Lenner P, Muti P, Shore RE, Johansson I, Krogh V, Lukanova A, Stattin P, Afanasyeva Y, Rinaldi S, Arslan AA, Kaaks R, Berrino F, Hallmans G, Toniolo P, Adlercreutz H, 2006 Circulating enterolactone and risk of endometrial cancer. Int. J. Cancer 119, 2376–2381. 10.1002/ijc.22140. [PubMed: 16929490]

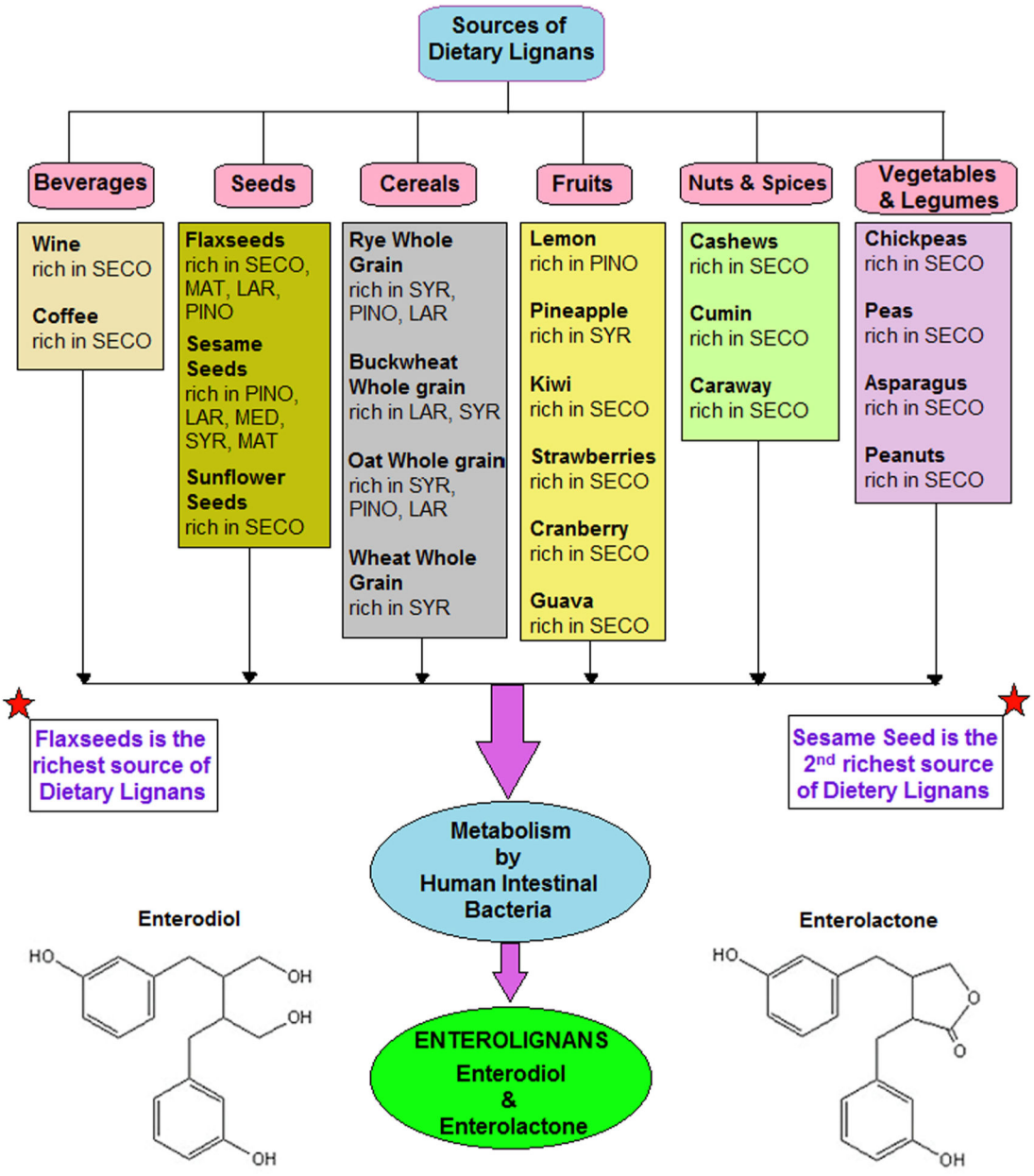

Fig. 1.

Metabolism of dietary lignans obtained from the major food sources to produce enterolignans in humans.

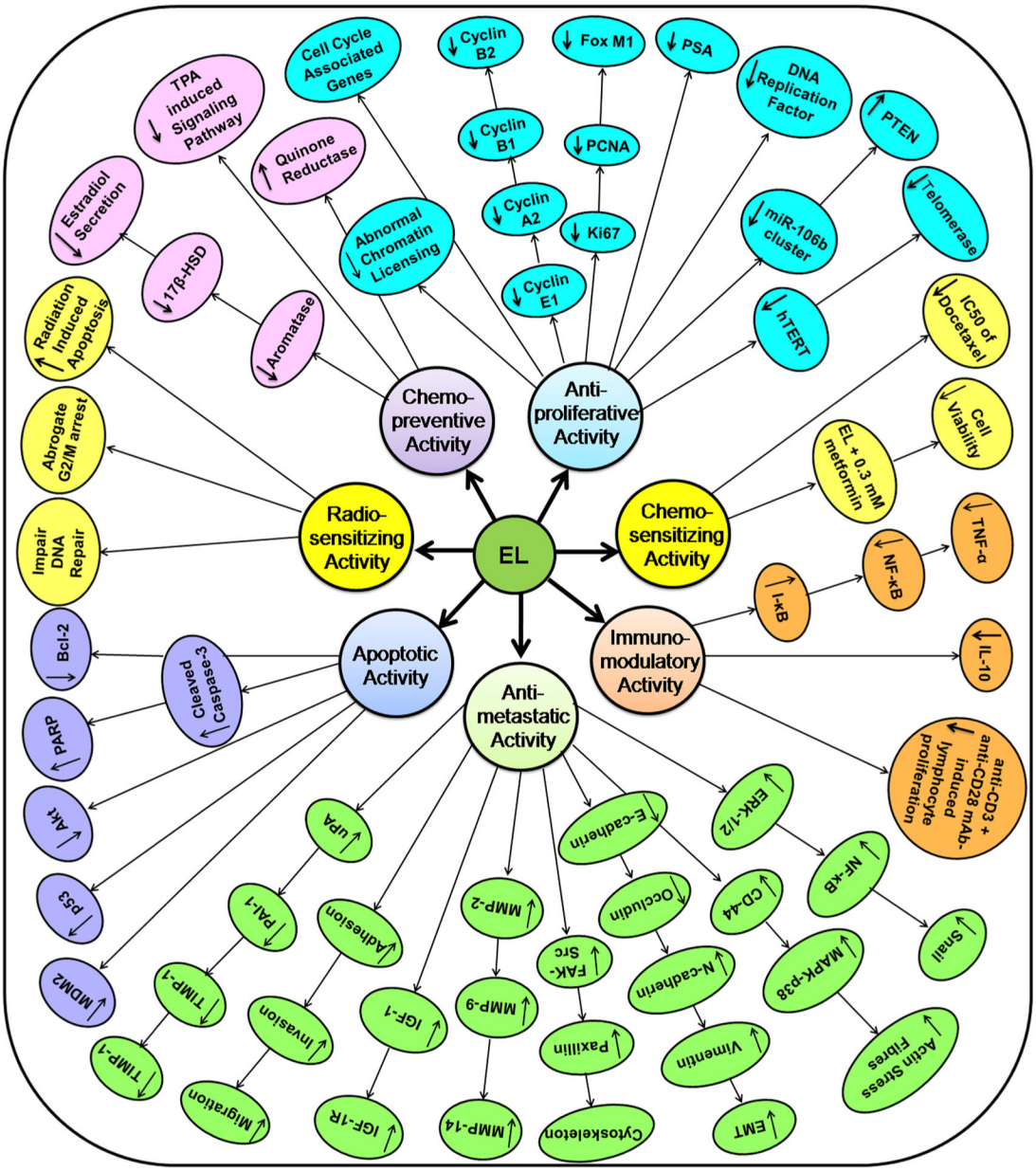

Fig. 2.

Anticancer activities of EL with several molecular targets and mechanistic endpoints investigated in breast, prostate, colon, lung, osteosarcoma, monocytic leukemia human cancer cell lines.

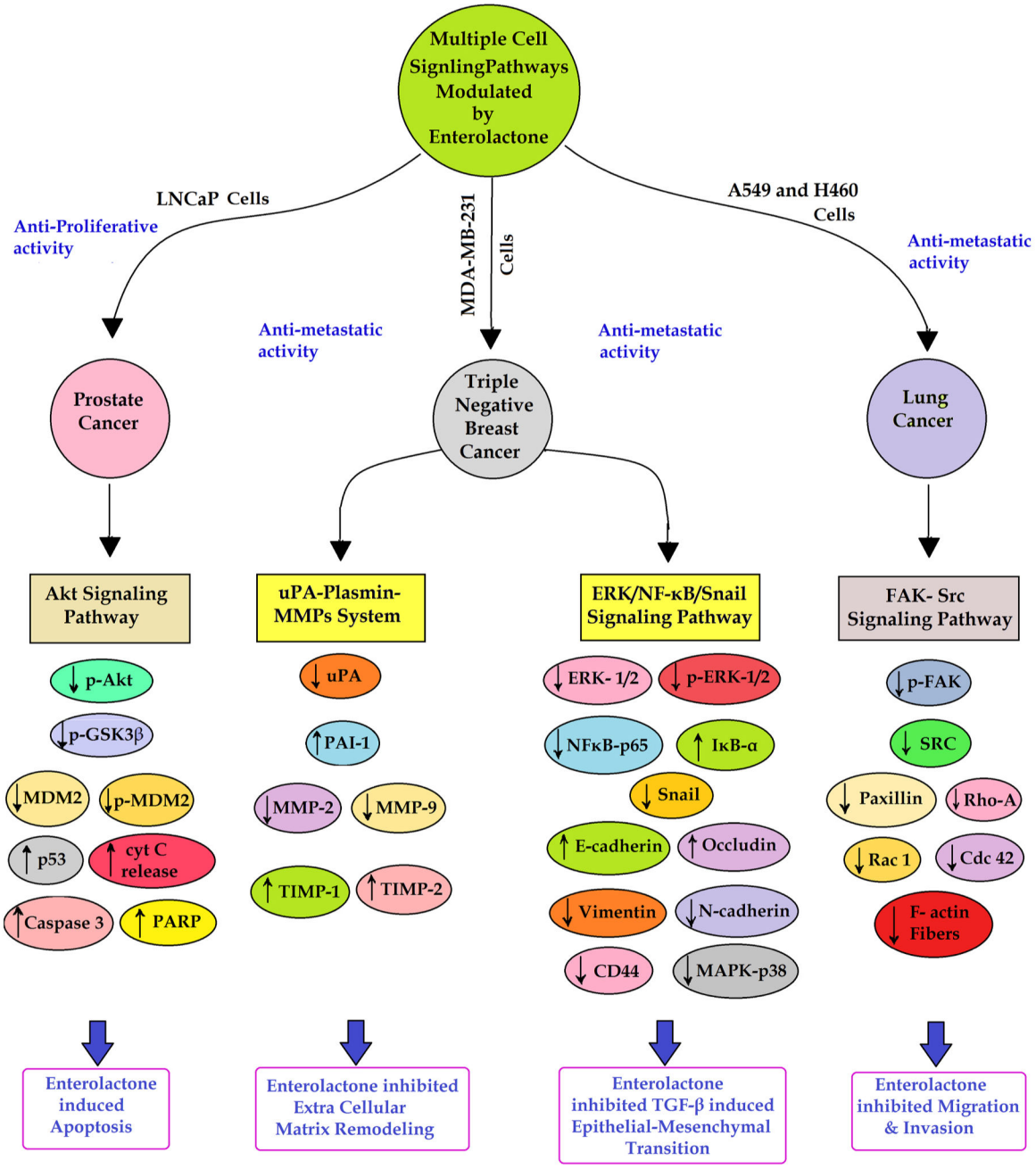

Fig. 3.

Major signaling pathways modulated by Enterolactone to arrest carcinogenesis and metastasis, particularly in breast cancer and lung cancer.

Table 1

Epidemiologic studies based on plasma/serum/urine Enterolactone concentrations and intake of Enterolactone in association with several cancer risks.

Types of cancer	Country/ Region	Design	Cases/ Controls	Methodology	Analysis of EL	Findings related to EL	Interpretation	Ref.
Breast cancer	Boston, USA	Dietary Study	10 omnivores, 10 vegetarians and 7 BC; PoM women	72 h collection of urine, 3-day food record.	Nutrient composition, Urinary EL and ED by capillary GC.	Urinary excretion of EL in the BC group was significantly lower than in both the other groups. ED excretion was also lower in the BC group than in the vegetarian group.	PoM women with BC excreted significantly less EL in their urine than did healthy PoM women	(Adlercreutz et al., 1982)
	Western Australia	CCS (RD)	144 /144 women	SQ and FFQ, 72 h urine collection, Blood sample collection before the treatment.	Urinary PhE, ED, EL and MAT by isotope dilution GC-MS.	High excretion of both equol and EL was associated with a substantial reduction in BC risk, with significant trends through the quartiles: equol ORs were 1·00, 0·45 (95% CI 0·20, 1·02), 0·52 (0·23, 1·17), and 0·27 (0·10, 0·69)—trendp = 0·009—and EL ORs were 1·00, 0·91 (0·41, 1·98), 0·65 (0·29, 1·44),0·36 (0·15, 0·86)—trend p = 0·013.	High intake of equol and EL could be important in the prevention of BC.	(Ingram et al., 1997)
	Eastern Finland	CCS (RD)	194 (68 PrM and 126 PoM)/208 women	FFQ, Serum samples collection before the examinations.	Serum EL by TR-FIA	The mean serum EL concentration in the lowest quintile was 3.0 nmol/l and 54.0 nmol/l in the highest (OR in the highest quintile of EL adjusted for all of the known risk factors for BC was 0.38 (95% CI, 0.18–0.77; P for trend, 0.03). The inverse association between serum EL and risk of BC was seen in both PrM and PoM women.	Serum EL level was significantly inversely associated with risk of BC	(Pietinen et al., 2001)
	Shanghai, China	CCS (RD)	250 /250 women	SQ and FFQ Urine samples collection before cancer therapy.	Urinary isoflavonoids, ED, EL, and citrus flavonoids by LC-MS	The risk of BC was reduced with increasing excretion of total isoflavonoids and total mammalian lignans (ED and EL). The risk of BC was reduced with increasing excretion of total isoflavonoids (P for trend, 0.04) and total lignans (P for trend, <0.01), with adjusted ORs of 0.62 (95% CI, 0.39–0.99) and 0.40 (95% CI, 0.24–0.64) observed for the highest versus the lowest tertile of total isoflavonoid and lignan excretion,	Study suggested that high intake of certain PhE like flavonoids and lignans (dietary precursors of ED and EL) may reduce the risk of BC	(Dai et al., 2002)
	Western New York, USA	CCS (RD)	96 / 86 PrM women 112 / 102l PoM women.	SQ and FFQ Blood samples collection Lignan intake = EL + ED production from foods.	Analysis of dietary lignans stratified by CYP17 genotype.	Women in the highest tertile of dietary lignans tended to have reduced breast cancer risk (OR 0.45, 95% CI 0.20–1.01 and OR 0.59, 95% CI 0.28–1.27, PrM and PoM women, respectively). Substantially reduced risks in the highest tertile of lignans were observed for PrM women with at least one A2 allele (OR 0.12, 95% CI 0.03–0.50).	Results suggested that CYP17 genotype may be important in modifying the effect on BC risk of ED and EL particularly for PrM women	(McCann et al., 2002)

Types of cancer	Country/ Region	Design	Cases/ Controls	Methodology	Analysis of EL	Findings related to EL	Interpretation	Ref.
	Western New York USA	CCS (RD)	315 / 593 PrM women 807/ 1443 PoM women.	Self administered 104-item FFQ Detailed in-person interviews.	ED and EL= SECO + MAT in diet.	PrM women in the highest quartile of dietary lignan intake had reduced breast cancer risk (OR= 0.66; 95% CI =0.44–0.98). No association was observed between lignan intakes and PoM BC.	Authors concluded that lignans may be important in the etiology of BC, particularly among PrM women.	(McCann et al., 2004)
	Southern Germany	CCS (RD)	278 /666 PrM women	SARFQ, Validated FFQ.	By establishing the database of PhE containing foods usually consumed in Europe.	Both estimated mammalian lignans, ED and EL were inversely associated with BC risk, with ORs (95% CI) of 0.61 (0.39–0.98) and 0.57 (0.35–0.92), respectively	Authors suggested an important role of dietary intake of daidzein and genistein, MAT, Ed and EL to reduce PrM BC risk in this study population.	(Linseisen et al., 2004)
	Denmark	CCS (RD)	381/381 PoM women	SQ and FFQ Blood samples collection	Plasma EL by TR-FIA	For estrogen receptor α-positive BC (n = 273) only a weak association was seen (IRR,0.97; 95% CI, 0.88-1.06), whereas for estrogen receptor α-negative BC (n = 80; IRR, 0.71; 95% CI, 0.53-0.94) a protective effect was seen per 20 nmol/L higher plasma EL.	Authors found a tendency toward a lower risk BC with higher concentrations of EL, which was restricted almost entirely to estrogen receptor α-negative BC	(Olsen et al., 2004)
	Genoa, Italy	Cohort Study (PD)	383 women with palpable cysts	Serum samples collection at the time of first cyst aspiration.	Serum EL by TR-FIA	Median values of serum EL were significantly lower in women who subsequently developed BC: 8.5 nM/l versus 16.0 nM/l: P = 0.04. OR for BC were: 0.36 (P = 0.03), 0.57 (P = 0.3) and 0.38 (P = 0.25) for 25th (8 nM/l), 50th (16 nM/l) and 75th (24 nM/l) percentile values, respectively.	Authors concluded that the serum EL concentration was inversely correlated with the risk of BC in women with palpable cysts.	(Boccardo et al., 2004)
	Southern Germany	CCS (RD)	220/ 237 PrM women	SARFQ and Validated FFQ, Blood samples collection.	Plasma EL by TR-FIA	PrM BC risk decreased with increasing plasma EL concentrations. Adjusted OR (95% CI) were 0.42 (0.20–0.90) and 0.38 (0.17–0.85) (P for trend 0.007) for women in the third and fourth quartile of plasma EL compared to those in the lowest quartile.	Authors concluded a strong inverse association between EL and PrM BC risk as found with dietary intake estimates.	(Piller et al., 2006)
Breast cancer	France	Cohort Study (PD)	1469 incident cases of primary invasive BC	SADHQ evaluating 208 food items.	Estimation of exposure to ED and EL from dietary lignan intake.	The inverse associations between PhE intakes and PoM BC risk were limited to estrogen receptor- and progesterone receptor-positive disease (e.g., RR for highest versus lowest quartiles of total plant lignan intake = 0.72, 95% CI = 0.58 to 0.88, P_{trend} = .01, 174 versus 214 cases per 100 000 person-years, and RR for highest versus lowest quartiles of total enterolignan (ED and EL) level = 0.77, 95% CI = 0.62 to 0.95, P_{trend} = .01, 164 versus 204 cases per 100 000 person-years)	High dietary intakes of plant lignans and high exposure to enterolignans (ED and EL) were associated with reduced risks of estrogen receptor and progesterone receptor positive PoM BC	(Touillaud et al., 2007)

Types of cancer	Country/ Region	Design	Cases/ Controls	Methodology	Analysis of EL	Findings related to EL	Interpretation	Ref.
	Sweden	Nested CCS (PD)	366 / 733 women	A modified diet history method, Direct anthropometric measurements, Blood samples collection.	Plasma EL by TR-FIA	EL concentrations above the median (16 nmol/L) were associated with reduced BC risk when compared with those below [OR, 0.75; 95% CI (95% CI), 0.58-0.98]. The reduced risk was only observed for estrogen receptor α (+); OR, 0.73; 95% CI, 0.55-0.97] and estrogen receptor β (−) tumors (OR, 0.60; 95% CI, 0.42-0.84), with significantly different risks for estrogen receptor β (−)and estrogen receptor β (+) tumors (P for heterogeneity = 0.04).	The protective association between EL and BC was significantly different between estrogen receptor β (−) and estrogen receptor β (+) tumors and most evident in tumors that express estrogen receptor α but not estrogen receptor β.	(Sonestedt et al., 2008)
	Germany	Meta Analysis	11 prospective cohort studies and 10 CCS (total 21 studies)	A systematic MEDLINE search to identify epidemiologic studies published between 1997 and August 2009.	Pooled risk estimates (REs) for total lignan exposure, dietary lignan intake, enterolignan exposure, and EL in blood or urine were calculated.	BC risk was also inversely associated with enterolignan exposure (4 studies; RE: 0.84; 95% CI: 0.71, 0.97) but not with blood or urine EL concentrations. The associations were not significantly different between Estrogen receptor-status subgroups (6 studies).	Authors concluded that high lignan exposure may be associated with a reduced BC risk in PoM women	(Buck et al., 2010)
	Germany	Follow-up Study	2653 PoM BC patients	A self-administered validated 176-items FFQ An intake in grams per day (g day–1) was calculated for each food item.	Bioavailable ED and EL were calculated per 100 g of ingested foods.	High estimated EL and ED levels were associated with significantly lower overall mortality (highest quintile, HR= 0.60, 95% CI= 0.40–0.89, P_{Trend}= 0.02 and HR= 0.63, 95% CI= 0.42–0.95, P_{Trend}= 0.02, respectively)	PoM BC patients with high estimated enterolignans (ED and EL) may have a better survival	(Buck et al., 2011a; 2011b)
	Denmark	Cohort Study (PD)	24,697 PoM women	FFQ, A lifestyle questionnaire, Plasma samples collection.	Plasma EL by TR-FIA	When comparing women with EL levels above the median (20.5 nmol/l) to those with lower levels, decreased HR were seen for both ACM (HR: 0.47; 95% CI: 0.32–0.68) and BCRM (HR: 0.56; 95% CI: 0.36–0.87).	Higher prediagnostic plasma levels of ELwere found related to lower mortality among BC patients.	(Olsen et al, 2011)
	Germany	Prognosis Study	1140 PoM BC patients	Clinical and pathologic records. Serum samples collection.	Serum EL by TR-FIA	Higher serum EL levels were associated with significantly reduced HRs for death (HR per 10 nmol/L increment, 0.94; P .04; HR for the highest quartile, 0.58; 95% CI, 0.34 to 0.99). The highest quartile of serum EL was associated with a significantly reduced risk of death only for estrogen receptor – tumors (HR, 0.27; 95% CI, 0.08 to 0.87).	PoM patients with BC who have high serum EL levels may have better survival.	(Buck et al., 2011a; 2011b)
	Italy	Cohort Study (RD)	300 Patients operated on for BC	Operation and subsequent follow up, Blood samples collection.	Serum EL by TR-FIA.	An association between a decreased mortality risk and EL levels ≥ 10 nmol/l was found in respect to both all-cause and breast cancer-specific mortality.	ED and EL might play an important role in reducing all-cause and cancer-specific mortality	(Guglielmini et al., 2012)

Eur J Pharmacol. Author manuscript; available in PMC 2020 June 05.

Types of cancer	Country/ Region	Design	Cases/ Controls	Methodology	Analysis of EL	Findings related to EL	Interpretation	Ref.
						BCRM risk remained constantly lower in those patients with higher EL levels.	of the patients operated on for BC.	
	Germany	CCS (RD)	1250/ 2164 PoM women	Self-administered FFQ, Serum samples collection.	Serum EL by TR-FIA.	Significant inverse association between serum EL and PoM BC risk, which was stronger for estrogen receptor− progesterone receptor− than for estrogen receptor + progesterone receptor + tumors but not differential by further expression of human epidermal growth factor receptor 2.	Study supported an inverse association between higher serum EL levels and PoM BC risk.	(Zaineddin et al.,2012)
	Germany	Prognosis Follow-up Study (PD)	2182 PoM BC patients	Clinical and pathologic records, Serum samples collection.	Serum EL by TR-FIA.	High EL concentrations were significantly associated with lower ACM (per 10 nmol L^{-1}: HR 0.94, 95% CI 0.90–0.98), BCSM(HR 0.94, 0.89–0.99), and DDFS (HR 0.94, 0.90–0.98).	Study showed that high lignan exposure (EL) is associated with reduced mortality in BC patients.	(Seibold et al., 2014)
Prostate cancer	Sweden	CCS (RD)	1499 / 1130 men Serum collection 209/214 men	FFQ Serum samples collection	Serum EL by TR-FIA	Intermediate serum levels of EL were associated with a decreased risk of PC. The ORs comparing increasing quartiles of serum EL concentration to the lowest quartile were, respectively, 0.28 (95% CI: 0.15–0.55), 0.63 (95% CI: 0.35–1.14) and 0.74 (95% CI: 0.41–1.32)	Results supported the hypothesis that certain foods high in PhE are associated with a lower risk of PC	(Hedelin et al., 2006)
	Scotland	CCS (RD)	433/483 men	A validated FFQ Blood samples collection.	Serum EL by isotope dilution GC-MS	A significant inverse associations was found with increased serum concentrations of EL (adjusted OR 0·40, 95% CI 0·22, 0·71) and with the consumption of soy foods (adjusted OR 0·52, 95% CI 0·30, 0·91).	Study supported the hypotheses that soy foods and EL protect against PC in older Scottish men.	(Heald et al., 2007)
	Scotland	CCS (RD)	247 PC/ 125 BPH/274 men	Serum samples collection, DNA extraction.	Serum EL by isotope dilution GC-MS	TT homozygotes who had low serum EL concentrations (below median) were more likely to have PC (OR= 2.90; 95% CI, 1.28–6.57) than individuals with CC/CT genotype and high serum EL concentrations (above median).	PC susceptibility was associated with TT genotype of SNP rs10993994 and increased risk of PC was modified by serum EL concentrations.	(Ho et al., 2012)
	USA	Multisite Phase II RCT	147 PC patients	30 g/day of whole-ground flaxseed supplementation for ~30 days before surgery. Pre and post surgery urine samples and tumor tissues collection.	Urinary EL by HPLC	Total urinary enterolignans and EL were significantly and inversely correlated with Ki67 in the tumor tissue (ρ= −0.217, P = .011, and ρ = −0.230, P = .007, respectively), and a near-significant inverse association was observed for ED (q =− 0.159, P = .064). An inverse association was observed between EL and VEGF (q= −0.143, P = .141),	Flaxseed-derived EL is inversely associated with tumor cell proliferation in men with localized PC	(Azrad et al., 2013)
	China	Meta-analysis	2 Cohort and 9 CCS on PhE intake and 8	Relevant publications were identified in the MEDLINE database	The ORs were used as the common measure	In stratified analysis, high genistein and daidzein intake and increased serum	Increased serum concentration of EL was associated with a	(He et al., 2015)

Types of cancer	Country/ Region	Design	Cases/ Controls	Methodology	Analysis of EL	Findings related to EL	Interpretation	Ref.
			studies on serum concentrations of PhE	using PubMed, Web of Science, and the Cochrane Library up to June 2014	of association across studies by considering the RRs as ORs.	concentration of EL were associated with a significant reduced risk of PC.	significant reduced risk of PC	
Endometrial cancer	Denmark	Case Cohort Study	173/149 women	SFQ, Blood samples collection.	Plasma EL by TR-FIA	A 20 nmol/l higher plasma concentration of EL was associated with a nonsignificant lower risk of EMC (IRR 0·93, 95% CI 0·84, 1·04)	Authors found some support for a possible inverse association between plasma EL concentration and EMC incidence.	(Aarestrup et al.,2013)
Colorectal cancer	Netherlands	CCS (RD)	532/503	SFQ, Blood samples collection.	Plasma EL by LC-MS	Plasma ED concentrations were associated with a reduction in CRA risk after adjustment for confounding variables, OR (95% CI) were 1.00, 0.69 (0.42-1.13), 0.60 (0.37-0.99), and 0.53 (0.320.88) with a significant trend (P = 0.01) through the quartiles. EL's reduction in risk was not statistically significant (P for trend = 0.09).	Substantial reduction in CRA risk among subjects with high plasma concentrations of enterolignans	(Kuijsten et al.,2006)
	United Kingdom	CCS (PD)	221/886	Prospective collection of lifestyle and 7-d records of diet	509 food items by LC-MS	Among women, CRC risk was inversely associated with EL (OR: 0.33; 95% CI: 0.14, 0.74) and total enterolignans (OR: 0.32; 95% CI: 0.13, 0.79), with a positive trend detected for SECO (OR: 1.60; 95% CI: 0.96, 2.69).	EL, found at high concentration in eggs and dairy products, may influence the risk of CRC among women.	(Ward et al, 2010)
	Denmark	Case Cohort Study	244 CoC/137 RC/370	Lifestyle questionnaire, A 192-item FFQ, Blood samples collection.	Plasma EL by TR-FIA	For each doubling in EL concentration there was lower risk of colon cancer among women [IRR (95% CI) = 0.76 (0.60–0.96)] and a tendency toward lower risk of rectal cancer [IRR (95% CI) = 0.83 (0.60–1.14)].	Study supported the hypothesis that EL may protect against colon cancer in women	(Johnsen et al., 2010)
Gastric cancer	Korea	CCS	462/670	Meta-analysis.	Plasma EL by TR-FIA	Risk allele of CRK rs7208768 had a significantly increased risk for gastric cancer at low PhE levels (p interaction ≤0.05).	Interaction between CRK gene and PhE modify gastric cancer risk.	(Yang et al., 2012)
Lung cancer	USA	CCS (RD)	1674/1735	FFQs Quantification of dietary intake of 12 individual PhE	Intake of specific PhE was calculated using the DIETSYS + Plus version 5.9 dietary analysis program.	High intake of the EL and ED and use of hormone therapy were associated with a 50% (OR, 0.50; 95% CI, 0.31-0.68; P = .04 for interaction) reduction in risk of lung cancer.	Study supported growing epidemiologic evidence that PhE (EL, ED) are associated with a decrease in risk of lung cancer	(Schabath et al.,2005)

CCS= Case Control Study, RD= Retrospective Design, PD= Prospective Design, PrM- Premenopausal, PoM= Postmenopausal, SQ = Structured Questionnaire, FFQ= Food Frequency Questionnaire, BC= Breast Cancer, PhE= Phytoestrogens, GC-MS = Gas Chromatography-Mass Spectroscopy, TR-FIA= Time Resolved-Fluoroimmunoassay, OR= Odds Ratio, CI= Confidence Interval, IRR= Incidence Rate Ratio, LC-MS = Liquid Chromatography-Mass Spectroscopy, SARFQ= self-administered risk factor questionnaire, SADHQ= Self-Administered Diet History Questionnaire, RR= Relative Risk, HR= Hazard Ratio, BCSS= Breast Cancer-Specific Survival, BCRM= Breast Cancer Related Mortality, BCSM= Breast Cancer Specific Mortality, BCUM= Breast Cancer Unrelated Mortality, ACM= All-Cause Mortality, PC= Prostate Cancer, BPH= Benign Prostatic Hyperplasia, RCT= Randomized Controlled Trial, SFQ= self-administrated questionnaires, HPLC= high-performance liquid chromatography, IHC= Immunohistochemistry, EMC= Endometrial Cancer, CRA= Colorectal adenoma, CRC= Colorectal Cancer, CoC= Colon Cancer, IRR= Incidence Rate Ratios, RC= Rectal Cancer.

Table 2

In vivo studies investigating the exclusive effects of EL in cancer bearing animal models.

Type of cancer	Experimental Cancer Model	Animals used	Dosing	ROA	Principle findings	Ref.
Breast cancer	DMBA induced mammary carcinoma	Female Sprague Dawley rats	EL 1 mg/kg and 10 mg/kg of BW starting 9 weeks after the DMBA-induction.	Oral	• EL at a dose of 10 mg/kg of body weight for 7 weeks significantly inhibited tumor growth. • The effect of EL was not restricted to any specific histological tumor type.	(Saarinen et al., 2002)
	MCF-7 human breast cancer xenografts	Ovariectomized athymic nude female mice	10 mg/kg body weight of EL, ED, GEN and mixture daily for 22 weeks.	SC	• In the EL and ED treated mice, palpable tumors regressed significantly. • Tumor cell apoptosis was significantly enhanced by the Ed and EL.	(Power et al., 2006a)
	MCF-7 human breast cancer xenografts	Ovariectomized athymic nude female mice	10 mg/kg body weight of EL, ED, Genistein and mixture daily for 22 weeks.	SC	• A significant positive correlation was observed between MCF– 7 tumor volume and femur BMD. • ED and EL did not exert adverse effects on bone and uterus health in a PoM breast cancer mouse model.	(Power et al., 2006b)
	MCF-7 human breast cancer xenografts	Female athymic mice, BALB/c nu/nu	Either 10% flaxseed diet or BD with daily injections of ED, EL (15 mg/kg BW).	SC	• Flaxseed, ED and EL counteracted E2-induced growth and angiogenesis in solid tumors. • In vivo extracellular VEGF was significantly decreased with Flaxseed, ED and EL interventions.	(Jungeström et al., 2007)
	MCF-7 human breast cancer xenografts	Ovariectomized athymic nude female mice	BD or BD supplemented with 100 mg/kg ENL, 100 mg/ kg GEN or their combination (EL + GEN).	Oral	• EL and EL + GEN inhibited E2-induced cancer growth and angiogenesis. • EL and EL + GEN decreased both stroma- and cancer cell-derived VEGF.	(Saarinen et ah, 2010)
	MCF-7 human breast cancer xenografts	Athymic female mice, Balb/cA nu/nu	BD or BD supplemented with 100 mg/kg ENL, 100 mg/ kg GEN or 10% ground flax. TAM (1 mg for every 2 days)	OralSC	• Tumors treated with TAM and fed Flax or EL exhibited decreased in vivo release of IL-1β derived from the murine stroma and decreased microvessel density. • TAM, Flax, and EL increased interleukin-1 receptor antagonist (IL-1Ra) levels significantly and decreased tumor angiogenesis.	(Lindahl et al., 2011)
	Gnotobiotic rat model (LCC rats) of DMBA induced breast cancer	Female germ-free Sprague Dawley rats	Flaxseed-rich diet, contained 0.34 g/kg SDG for 13 weeks	Oral	• The lignan SDG was converted into the enterolignans ED and EL in the LCC rats. • Results were not in favor of an estrogen-dependent mechanism as an explanation for the protective effects of enterolignans.	(Mabrok et al., 2012)

Type of cancer	Experimental Cancer Model	Animals used	Dosing	ROA	Principle findings	Ref.
					• ED and EL lowered tumor burden in a gnotobiotic rat model of breast cancer.	
	Knockout ABCG2$^{-/-}$ and wild-type	Lactating female mice	BD supplemented with 1% of lignan-rich extract (SDG = 2 mg/g) for 7 days	Oral	• EL and ED levels were higher in plasma and lower in milk from ABCG2$^{-/-}$ compared with wild-type mice. • Both ED and EL were accumulated in the mammary glands which could exert chemopreventive effects against breast cancer. • ABCG2 may be determinant for plasma and milk levels of enterolignans.	(García-mateos et al., 2017)
	ES-2 human ovarian cancer xenografts	BALB/c nude mice	ED or EL at 1 mg/kg or 0.1 mg/kg separately, once per 2 days up to 32 days.	ITI	• ED and EL significantly reduced the tumor volume in mice. • EL had higher anticancer activities and fewer side effects in the animals than ED at the same concentrations.	(Liu et al., 2017)
Liver cancer	Subcutaneous AH109A Hepatomas in Rats	Male Donryu rats	Basal diet or basal diet supplemented with either 0.15% of HMR for 14 days or 0.001% and 0.01% of EL, for 21 days.	Oral	• Both HMR and its metabolite EL reduced the growth and metastasis of solid AH109A hepatomas in rats.	(Miura et al., 2007)
Uterine carcinogenesis	N-ethyl-N′-nitro-N nitrosoguanidine (ENNG), induced uterine carcinogenesis	Female Crj: Donryu rats	From 11th weeks of age animals were fed with 200 (11 ± 0.3 mg/kg/day), or 600 (32.7 ± 1.1 mg/kg/day) ppm HMR until 15 months of age.	Oral	• Incidences of uterine adenocarcinoma in both HMR-dosed groups were significantly reduced. • From urinalysis, HMR was metabolized mainly to EL and hydroxyenterolactone (hEL). • HMR or its metabolites (EL&hEL) exert chemopreventive effects in the rat ENNG-uterine carcinogenesis model.	(Katsuda et al., 2004)
Colon cancer	Colo 201 human colon cancer xenografts	Male BALB/c-nu/nu mice	EL at a dose of 0, 1, or 10 mg/kg of body weight 1 day before tumor cell inoculation and treatment was continued 3 times a week for 23 days	SC	• EL inhibited the growth of colo 201 cells, as evaluated by tumor volume. • Cell proliferation, as indicated by PCNA labeling, was significantly lower in the EL treated groups. • Cell death, as reflected by the TUNEL index, was significantly higher in the EL treated groups.	(Danbara et al., 2005)

ROA = Route of Administration, BW = Body Weight, DMBA = 7, 12-Dimethylbenz(a) anthracene, HMR = Hydroxymatairesinol, SC = Subcutaneous, GEN = Genistein, BMD = Bone Mineral Density, PoM = Postmenopausal, E2 = Estradiol, BD = Basal Diet, VEGF = Vascular endothelial growth factor, TAM = Tamoxifen, IL-1Ra = Interleukin-1 Receptor Antagonist, BCRP/ABCG2 = Breast Cancer Resistant Protein, ITI = Intra Tumor Injection.

Table 3

In vitro studies investigating the effect of EL in several human cancer cell lines.

Activity	Cancer	Experimental Human Cell Culture Model	Dose and Treatment Period of EL	Mechanistic Endpoints of EL Investigated	Potential Mechanism(s) of EL	Ref
Chemopreventive activity	CC	JEG-3	1, 10 and 100 μM	• EL inhibited intracellular aromatase activity.	EL acts as an aromatase inhibitor.	(Adlercreutz and Vickery, 1993)
	BC	MDA-MB-468	100 μM EL for 30 min.	• Reduced TPA-induced *c-fos* transcription. • IC_{50} of EL was 41 μM in MDA-MB468 BC cells.	EL interfere with TPA-induced signal transduction pathway.	(Dale et al., 1998)
	CoC	Colo 205	0.001 and 10 μM for 48 h	• EL significantly carried out conc. dependent induction of QR activity. • EL significantly induced QR mRNA • At high conc. EL inhibited the cell growth by showing toxicity.	EL is capable of QR induction in Colo205 cells by promoting QR mRNA expression.	(Wang et al., 1998)
	BC	MCF-7	1–50 μM for 6 h to 5 days	• EL significantly decreased the amount of estrone (E1) produced via the aromatase pathway. • EL significantly inhibited estradiol (E2) production via 17β-HSD pathway. • EL reduced MCF-7 cell proliferation	EL modulates E2 synthesis via inhibiting aromatase and 17β-HSD in estrogen receptor + BC cells	(Brooks and Thompson, 2005)
	BC	T-47D T47D-KBluc	10 μM for 24 h	• EL showed the highest inhibitory effect on ERE activation by E2.	EL possesses antiestrogenic activity.	(Pianjing et al., 2011)
	ChoC BC	JEG-3, BeWo MCF-7	10–100 μg/ml over 72 h	• EL downregulated the expression of estrogen receptor α and progesterone receptor in a dose dependent manner in MCF-7 cell line. • EL inhibited estradiol secretion in JEG-3 cells while induced in BeWo and MCF-7 cells in a dose dependent manner.	EL may exhibit chemopreventive activity in estrogen receptor + BC.	(Schröder et al., 2016)
Antiproliferative activity	CoC	LS174T, Caco-2, HCT-15, T-84	100 μM for 8–10 days	• EL reduced the proliferation of all cell lines. • EL was more than twice as effective as ED at same conc.	EL inhibits the growth of colon cancer cells through a mechanism other than antiestrogenic activity.	(Sung et al., 1998)
	OS	MG-63	0.01–10 mg/ml for 7 days	• EL inhibited the growth of cells.	EL exhibits antiproliferative effect on OS cells.	(Feng et al., 2008)
	PC	PC-3, DU-145, LNCaP.	10–100 μM for 72 h	• EL significantly inhibited the growth of all cell lines.	EL suppresses the growth of PC cells via hormonally	(Lin et al., 2001)

Activity	Cancer	Experimental Human Cell Culture Model	Dose and Treatment Period of EL	Mechanistic Endpoints of EL Investigated	Potential Mechanism(s) of EL	Ref
				• EL was a more potent growth inhibitor than ED. • IC_{50} of EL was 57 μM in LNCaP cells.	dependent and independent mechanisms.	
	PC	LNCaP	0–100 μM for 24 h to 6 days	• EL reduced cell density, metabolic activity, secretion of PSA and induced apoptosis. • EL beneficially regulated several key genes in PC.	EL exhibits an antiproliferative effect as a consequence of altered expression of cell cycle associated genes.	(McCann et al., 2008)
	PC	RWPE-1, WPE1-NA22, WPE1-NB14, WPE1-NB11, WPE1-NB26, LNCaP, PC-3	0.01–10 μM for 24–72 h	• EL inhibited the abnormal proliferation of the WPE1-NB14 and WPE1-NB11 cell lines by decreasing expression of abnormal chromatin licensing and DNA replication factor 1.	EL exhibits antiproliferative effect on PC cells.	(Mccann et al., 2013)
	PC	RWPE-1, WPE1-NA22, WPE1-NB14, WPE1-NB11, WPE1-NB26, LNCaP	10 to 100 μM over 48 h	• EL reduced the viability, restricted cell cycle and induced apoptosis in mid to later stage PC cell lines. • EL altered the expression of DNA licencing genes in mid to later stage PC cell lines. • EL repressed the expression of the miR-106b cluster leading to increased PTEN Expression.	Antiproliferative effects of EL in earlier stages of PC are mediated, in part, by microRNA-mediated regulation.	(McCann et al., 2014)
	BC	MCF-7 BT-20	1×10^{-3} to 1×10^{-7} mol/l for 24 h	• EL inhibited cell growth in both cells.	EL inhibits proliferation in BC cells.	(Abarzua et al., 2012)
	BC	MCF-7	1–100 μM for 48 h	• EL decreased cell viability, hTERT protein levels and telomerase activity (at 100 μM).	High concentration of EL inhibits the expression and activity of telomerase in BC cells to decrease viability.	(Ilbeigi et al., 2017)
	NSCLC	A549 H441 H520 Hs888Lu	0–100 μM for 24 to 72 h	• EL inhibited both short term and long term proliferation of NSC LC cells while did not affect the proliferation of normal lung cells. • EL suppressed LC cell proliferation through G1-phase cell cycle arrest by modulating G1-phase cell cycle regulatory genes and proteins.	EL inhibits cell proliferation by inducing G1-phase cell cycle arrest in NSCLC cells by down-regulating-cyclins and cyclin-dependent kinases	(Chikara et al., 2017b)
Apoptotic activity	CoC	Colo 201	2–100 μM for 24–72 h	• EL suppressed colo 201 cell growth (IC_{50} for 72 h: 118.4 μM) in vitro. • EL down-regulated apoptosis suppressing protein (Bcl-2) while up-regulated apoptosis-enhancing protein (cleaved form of Caspase-3) .	EL Induces apoptosis and inhibits growth of Human CoC cells.	(Danbara et al., 2005)

Activity	Cancer	Experimental Human Cell Culture Model	Dose and Treatment Period of EL	Mechanistic Endpoints of EL Investigated	Potential Mechanism(s) of EL	Ref
	CoC	SW480	0–200 μM for 24–72 h	• EL showed dose and time dependent decrease in cell number. • EL arrested the cell cycle at S-phase. • EL increased percentage of apoptotic cells.	EL inhibits CoC cell growth via cytostatic and apoptotic mechanisms.	(Qu et al, 2005)
	CoC	CaCo-2	50–150 μM for 24–72 h	• EL caused a significant increase in apoptotic cells and decrease in cell Proliferation.	EL inhibits proliferation and induces apoptosis in CoC cells.	(Bommareddy et al., 2010)
	PC	LNCaP	0–100 μM for 24–72 h	• EL decreased cell viability. • EL induced cell apoptosis. • EL Disrupted mitochondrial membrane potential and leads to cytochrome-c release. • EL induced cleavage of caspase-3 and PARP. • EL inhibited Akt activation. • EL promoted p53 expression and inhibited MDM2 Expression	EL suppresses LNCaP cell growth by the induction of apoptosis via a mitochondrial mediated, caspase-dependent pathway which may be mediated by the inhibition of Akt-dependent phosphorylation and promotion of p53 expression.	(Chen et al., 2007)
Antimetastatic activity	BC	MDA-MB-435, MDA-MB-231	1 to 10 μM for 24 h	• EL reduced human BC cell adhesion, invasion and migration in vitro.	EL, ED and TAM, alone or in combination, can inhibit the steps involved in the metastasis cascade.	(Thompson, 2003)
	PC	PC-3	0–80 μM for 20–24 h	• EL inhibited IGF-1-induced tyrosine phosphorylation of insulin-like growth factor-1 receptor (IGF-1R) and downstream signaling of insulin-like growth factor-1 receptor. • EL inhibited IGF-1-stimulated proliferation and migration of PC-3 cells.	EL suppresses proliferation and migration of PC cells through inhibition of IGF-1/ insulin-like growth factor-1 receptor signaling.	(Chen et al., 2009)
	BC	MCF-7 MDA-MB-231	25–75 μM for 24–48 h	• EL inhibited cell migration of MDA-MB-231 cell line. • EL disrupted actin cytoskeleton in MDA-MB-231 cell line. • EL downregulated MMP-2, 9 in both cell lines while MMP-14 in MDA-MB-231 cell line.	EL exhibits in-vitro antimetastatic activity in BC cells.	(Mali et al, 2012)
	BC	MDA-MB-231	0–400 μM over 48 h	• EL showed an antiproliferative effect (IC_{50} = 261.9 ± 10.5 μM for 48 h) by reducing the expression of cell proliferation related genes; Ki67, PCNA, and FoxM1.	EL shows antitumor effect by regulating the expression of genes associated with cell proliferation and the cell cycle. EL shows antimetastatic effect	(Xiong et al., 2015)

Activity	Cancer	Experimental Human Cell Culture Model	Dose and Treatment Period of EL	Mechanistic Endpoints of EL Investigated	Potential Mechanism(s) of EL	Ref
				• EL arrested the cell cycle in S phase, and a lower expression of Cyclin E1, Cyclin A2, Cyclin B1, and Cyclin B2 genes. • EL interfered with the cytoskeleton by downregulating phosphorylation of the FAK/ paxillin pathway, inhibiting migration and invasion of cells.	by blocking the FAK/paxillin signaling pathway.	
	BC	MDA-MB-231	25–75 μM for 24–72 h	• EL exhibited anticancer and antiproliferative effects on metastatic BC cells (IC_{50} = 73.00± 2.83 for 48 h). • EL inhibited colony formation and migration of BC cells in-vitro. • EL down-regulated the expression of uPA, MMP-2, MMP-9 genes while up-regulated PAI-1, TIMP-1, TIMP-2 genes. • EL also reduced the proteolytic activities of gelatinases MMP-2 and MMP-9 in BC cells to inhibit ECM remodeling.	EL suppresses proliferation, migration and metastasis of MDA-MB-231 breast cancer cells by inhibiting uPA induced plasmin activation and MMPs mediated ECM remodeling	(Mali et al., 2017)
	BC	MDA-MB-231	25–75 μM for 48 h	• EL arrested the growth of BC cells in the '*S*' phase and triggered apoptosis via caspase-3 activation. • EL inhibited TGF-β-induced migration and invasion in BC cells, in-vitro. • EL inhibited the TGF-β-induced EMT program by down-regulating vimentin and N-cadherin while up-regulating E-cadherin and Occludin in BC cells. • EL reduced the formation of actin stress fibers by inhibiting the expression of CD44 and MAPK-p38. • EL inhibited the ERK/NF-κB/Snail signaling in TGF-β-induced BC cells.	EL exhibits an antimetastatic activity in triple-negative BC via inhibiting the ERK/NF-κB/ Snail signaling pathway to revert TGF-β-induced EMT.	(Mali et al, 2018)
	LC	A549H460	0–100 μM for 24–48 h	• EL inhibited migration and invasion of LC cells in-vitro. • EL affected cytoskeleton in LC cells by decreasing the % of polymerized F-actin fibers and average length of F-actin fibers. • EL also reduced the number and size of focal adhesions in LC cells. • EL altered the expression of key transcripts associated with cell motility.	EL shows antimetastatic potential by altering FAK-Src signaling and suppressing invasion, migration of LC cell lines.	(Chikara et al., 2017a)

Activity	Cancer	Experimental Human Cell Culture Model	Dose and Treatment Period of EL	Mechanistic Endpoints of EL Investigated	Potential Mechanism(s) of EL	Ref
				• EL modulated FAK-Src signaling and inhibited phosphorylation of paxillin and Rho proteins in LC cells.		
	OC	ES-2	10^{-3} to 10^{-6} mol/L for 24–72 h	• EL inhibited the ovarian malignant properties including cancerous proliferation, invasion, and metastasis (EL was more effective than ED).	EL possesses a more effective anti-cancer capability and less side effects than ED.	(Liu et al., 2017)
Immunomodulatory Activity	ML CoC	PBL THP-1 CaCo-2	1–1000 μM for 24–72 h	• EL decreased a LPS induced TNF-α and IL-10 release in PBL (IC_{50} for TNF-α release was 430 μM). • EL suppressed anti-CD3 plus anti-CD28 monoclonal antibody-induced lymphocyte proliferation. • EL showed dose-dependent inhibition of cell proliferation and cytokine production in all cells. • EL prevented I-κB degradation and NF-κB activation which in turn decreased TNF-α in THP-1 cells.	EL modulates the immune response by acting on NF-κB signaling.	(Corsini et al., 2010)
Radiosensitizing activity	BC	MDA-MB-231 T47D	0–500 μM over 48 h	• EL significantly enhanced radiosensitivity of cells by abrogating G2/M arrest, impairing DNA repair, and increasing radiation-induced apoptosis. • EL increased chromosomal damages and aberrations in cells treated with EL combined with X-rays than X-ray alone.	EL acts as a novel radiosensitizer for BC irrespective of estrogen receptor status.	(Bigdeli et al., 2016b)
Chemosensitizing activity	BC	MDA-MB-231 SKBR3	3.12–1,000 μM for 72 h	• EL decreased the IC_{50} values of docetaxel in both cells while 50 μM EL significantly reduced cell viability when combined with 0.3mM metformin.	EL acts as a novel chemosensitizer for BC irrespective of receptor status.	(Di et al., 2018)

CC= Choriocarcinoma, BC= Breast Cancer, TPA= Phorbol Ester 12-O-tetradecanoylphorbol-13-acetate, IC_{50} = The half maximal inhibitory concentration, CoC= Colon Cancer, QR = NADPH:quinone reductase, conc. = concentration, PC= Prostate Cancer, TAM= Tamoxifen, 17β-HSD= 17β-hydroxysteroid dehydrogenase, ERE= Estrogen Responsive Element, PCNA= Proliferating Cell Nuclear Antigen, PARP= poly(ADP-ribose)-polymerase, OS= Osteosarcoma, PSA= Prostate Specific Antigen, PTEN= Phosphatase And Tensin Homolog, hTERT= Human Telomerase Reverse Transcriptase, NSCLC= Non Small Cell Lung Cancer, IGF-1R= Insulinlike Growth Factor-1 Receptor, ACC= adrenocorticocarcinoma, ML= Monocytic Leukemia, PBL= Peripheral Blood Leukocytes, I-κB= Inhibitory-κB, NF-κB= Nuclear Factor-κB, TNF-α= Tumor Necrosis Factor-α, ChoC= Chorion Carcinoma, PR= Progesterone Receptor, LC= Lung Cancer, OC= Ovarian Cancer, MDM2= Mouse Double Minute 2 homolog, IGF-1= Insulin-like Growth Factor-1, MMP= Matrix Metalloproteinases, PCNA= Proliferating Cell Nuclear Antigen, FoxM1 = Forkhead box protein M1, FAK= focal adhesion kinase, uPA= Urokinase Plasminogen Activator, PAI= Plasminogen Activator Inhibitor-1, TIMP= Tissue Inhibitor of Metalloproteinases, ECM= Extracellular Matrix, TGF-β= Transforming Growth Factor β, EMT= Epithelial-Mesenchymal Transition, CD44= Cluster of differentiation 44, MAPK-p38= mitogen-activated protein kinase-p38, ERK= Extracellular Signal-Regulated Kinase, NF-κB= nuclear factor kappa-light-chain-enhancer of activated B cells, LPS= Lipopolysaccharide, TNF-α= Tumor necrosis factor, I-κB= Inhibitor kappa b alpha.