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SHORT REVIEW

Chemopreventive Potential of Phytoestrogens on Hormone-Sensitive Cancer - An Updated Review

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Abstract

Hormone-dependent cancers contribute to the majority of cancer deaths in women. Treatment options for hormonal cancer such as breast, endometrial, prostate, and ovarian cancer aim at inhibiting key signalling pathways and hormones responsible for cell proliferation. Hormonal therapies in the long run cause musculoskeletal disorders, Disease reoccurrence, and drug resistance. There is a need for new alternative therapies to prevent and treat hormonal carcinomas. Phytoestrogens, a naturally occurring polyphenol have potent effects on hormonal cancers due to their estrogenic effects. Evidence suggests that phytoestrogens exert their apoptotic potential by interfering with steroidogenesis, gene expressions, and down-regulation of Protein Tyrosine Kinases, Matrix Metalloproteinases. They also act as topo-poisons. This review explains the key mechanisms of phytoestrogens in inhibiting cell proliferation in hormonal cancers by evidence from recent clinical studies, meta-analyses, and cohort study reports. Phytoestrogens have multi-target potential with both preventive and treatment properties on cancer cell lines. Combination therapies with phytoestrogens are more beneficial in controlling cell progression. Hence further research is required to explore their epigenetic properties on tumour suppressor genes which stay an important target in cancer research.

Keywords: Breast Cancer, Chemoprevention, Endometrial Cancer, Ovarian Cancer, Phytoestrogens

1. Introduction

Dietary phytoestrogens are naturally occurring non-steroidal polyphenols that exert estrogenic effects by binding to estrogen receptors due to their structural similarity with estrogens. Phytoestrogens are prevalent in legumes, soy products, flax seeds, sesame seeds, grains, and pulses. They are present at low traces in fruits and vegetables. Coumestanes, Stilbenes, Lignans, Isoflavonoids, and flavonoids are known to be the important groups of phytoestrogens. Extensive *in vitro* and *in vivo* evidence suggests that phytoestrogens have chemopreventive properties in hormone-sensitive cancers. They exhibit their apoptotic potential by interfering with steroidogenesis, protein tyrosine kinase, matrix metalloproteinases, Aromatase, and vascular endothelial growth factors. A case-control study done on three races of population noted that women with the highest tertiles of childhood soy intake significantly showed a reduced risk of breast cancer[1].

Phytoestrogens such as resveratrol analogues showed inhibition of Cyclin-Dependent Kinase which expresses a regulatory subunit called Cyclin D_1. Cyclin D_1 is correlated to Estrogen Receptor (ER) positive breast

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cancer which is often expressed in 50-80 % of breast cancers. Phytoestrogens also cause the induction of P_{53} transcription factors which is called the guardian of genome[2]. Apart from estrogenic effects, phytoestrogens express anti-androgenic effects that stay as a primary treatment strategy for prostate cancer. Studies show that a high intake of genestein and diadzein was significantly associated with decreased risk of prostate cancer due to the increased serum concentration of enterolactons[3]. A case-control study that was carried out on 500 women diagnosed with endometrial cancer revealed that there was a significant association between their dietary intake and cancer risk. Women who consumed a low amount of phytoestrogens had a higher risk of endometrial cancer compared to women who take a high intake of isoflavones[4]. The flavones and isoflavones are known to inhibit aromatase a key enzyme that converts androgens to estrogens in over 60% of breast carcinomas[5]. Thus Reports suggest that dietary estrogens play a significant role in cell signalling pathways and prevent cell proliferation. Phytoestrogens exhibit epigenetic properties such as chromatin modelling, DNA methylation, and gene expression which induces apoptosis on various carcinomas. In this study, the chemopreventive role of phytoestrogens on hormonal and reproductive cancers is explored by giving primary importance to clinical studies carried out on phytoestrogens.

2. Mechanistic Role of Phytoestrogens

2.1 Effects of Phytoestrogens on Cell Signaling Pathways

Phytoestrogens act on various cellular signalling pathways and exert their inhibitory potential in cancer cells. One such important role is the inhibition of Receptor Tyrosine Kinase (RTK) which plays a pivotal role in the tumour microenvironment by initiating signalling cascades through various pathways[6]. The RTK has an extracellular ligand-binding domain and an intracellular tyrosine kinase domain separated by a transmembrane domain[7]. The cytoplasmic region of RTK contains the protein Tyrosine Kinase (TK) domain, Juxtamembrane domain, and Carboxy-(c)-terminal domain. The tyrosine kinase domain phosphorylates tyrosine residues[8]. The RTKs get activated when there is a ligand binding which causes receptor dimerization and phosphorylation of RTK. The phosphorylated RTK further phosphorylates signalling molecules and activates intermediaries such as the Pi3K/AKT/mTOR pathway that induces cell growth and metabolism. The RAS/MAPK pathway also gets activated as a result of RTK phosphorylation that acts as a key regulator of cell proliferation, differentiation, and migration. Another important kinase that belongs to the Mitogen-Activated Protein Kinase (MAPK) family is called Extracellular signal-Regulated Kinase (ERK), which plays a role in transmitting extracellular signals to intracellular targets[7]. RTKs further transduce signals to STAT that controls the signals activated by lymphokines, the Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), and the Epidermal Growth Factor (EGF) that are involved in the cell survival mechanisms. molecules targeting RTKs are used as a first or second-line therapy in different types of cancer since 2001[8]. RTK inhibitors generally target the active site of the kinase and prevent the phosphorylation of intracellular targets. The RTKs mediate drug resistance through mutation and overexpression of oncogenic characters. Drugs developed by targeting protein tyrosine kinase have shown improved clinical outcomes but are limited to their toxicity. Phytoestrogens play a prominent role in inhibiting kinases. Genestein and Quercetin are naturally occurring PTK inhibitors that arrest the G2/M phase and cause suppression of tyrosine kinases[9]. In addition quercetin, luteolin, Genestein, and resveratrol cause downregulation of the PI3K-AKT pathway and CK_2 inhibition[10]. Diadzein and its metabolite equol suppress MEK1 Kinase activity which is responsible for cell transformation[11]. Wogonin was found to be the most potent inhibitor of cyclin-dependent kinases at nanomolar concentration[12]. PIM1 Kinase is known to be a true oncogene that is overexpressed in leukaemias, lymphomas, and prostate cancer. Quercetagetin a flavonoid found in marigolds is reported to inhibit PIM1 kinases and inhibited cellular proliferation[13] (Figure 1).

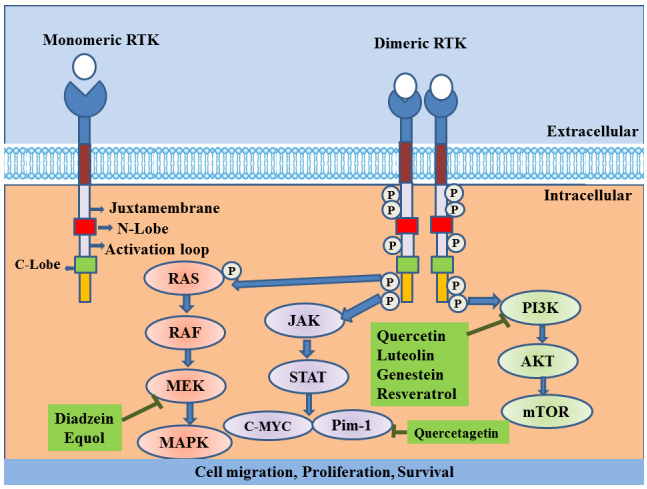

Figure 1. Inhibitory role of phytoestrogens in cell signalling pathways.

2.2 Role of Phytoestrogens in Inhibiting Nuclear Enzymes

The progression of cancer is closely correlated with the alterations in nucleases. The phosphodiester bonds between the ribose moieties are degraded by a group of enzymes called nucleases which are classified as DNases, RNases, and RNA. They act as a guardian of the genome and have a potential role in DNA replication and translation. Nucleases remain active intracellularly and extracellularly and can be a preferential target for various cancer therapies. One such important enzyme is the Flap endonuclease1 (FEN1) which is a key regulator of genome stability through DNA repair[14]. Overexpression of FEN1 is associated with various cancers. Overexpression of FEN1 was found to have a positive correlation with Breast, Uterine, and Prostate cancer. Inhibiting the FEN1 expression killed BRCA1 and BRCA2 mutant cancer cell lines without BRCA1 or BRCA2 defects[15]. Phytoestrogens such as Resveratrol, Quercetin, and Curcumin decrease the FEN1 expression through activation of the Nuclear Factor Erythroid 2 (NFER2) – related factor 2 (Nrf2). Nrf2 is a key regulator of the cellular antioxidant defence system which prevents the binding of FEN1 and causes DNA damage (Figure 2).

The Apurinic/apyrimidinic endonucleases 1 (APE1) Redox effector factor-1 (Ref-1) has a key role in the cell survival pathway. These multifunctional enzymes help in maintaining the genome integrity in more than 95% of cancer cells. The APE1/Ref-1 gets activated as a part of the DNA repair response through the Base Excision Repair Pathway (BER)[16]. Phytochemicals such as curcumin, resveratrol, diadzein, and epigallocatechin gallate (EGCG) are known to alter the expression of these enzymes. The down-regulating mechanism of these phytoestrogens is not known[17].

Phytoestrogens competitively target Estrogen Receptors and reduce the expression of estrogens by targeting various enzymes. Phytoestrogen reduces the expression of the aromatase enzyme that is involved in the conversion of androgens to oestrogens. The intratumoral stromal cells in breast cancer show the highest aromatase activity[18]. The more potent aromatase inhibitors amongst the phytoestrogens are flavones and flavanones. Apigenin inhibits aromatase activity at 0.1 μM. They also show their inhibitory effects on 17β-Hydroxysteroid dehydrogenases (17β-HSDs) that catalyze the conversion of androstenedione and oestrone to testosterone and oestadiol. The expression of 17β-HSDs is predominant in breast carcinoma cells[19]. Chrysin, apigenin, naringenin, and coumestrol inhibits the expression of 17β-HSD at micromolar doses. Enterolactones are also reported to have inhibitory potential against the conversion of estrone to oestrodiol at 10 and 1μM concentrations.

Phytoestrogens act on topoisomerase which stays an important target for the treatment of various carcinomas. Human topoisomerase releases helical tension to DNA tension to DNA molecules by inducing transient type 1 topoisomerase (single-stranded) and type 2 topoisomerase (double-stranded) breaks[19]. Phytoestrogens such as biochanin and genestein are reported to inhibit topoisomerase IIβ with enhanced DNA cleavage property[20]. A study conducted with Catechins and their derivative epigallocatechin showed potent inhibition on Topoisomerase I and II. Fisetin and diosmetin are reported to cause DNA cleveage[10]. Resveratrol is associated with increased expression of phosphorylated γH2AX an important biomarker for DNA double-strand breaks and involves in arresting S Phase. The recombinant human topo 2 is also inhibited by resveratrol[21]. This evidence suggests that phytoestrogens can act as topo poisons.

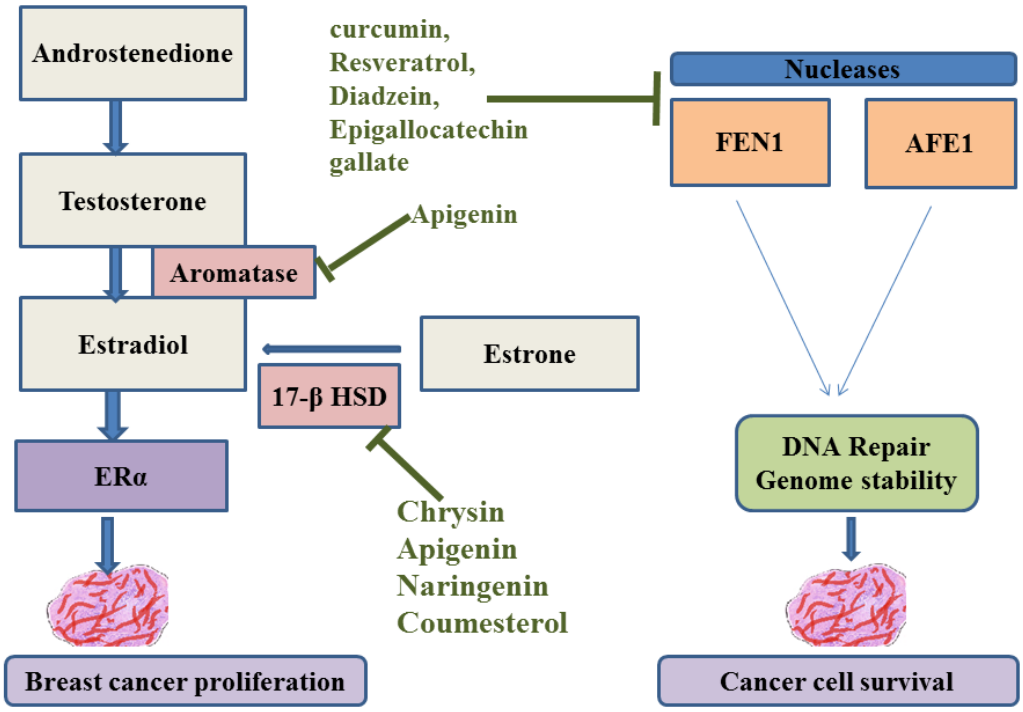

Figure 2. Inhibition of Aromatase and 17-β HSD, the key enzymes in estrogen synthesis by phytoestrogens. They also act upon FEN1 and APE1, the guardians of genomes.

2.3 Phytoestrogens as an Epigenetic Modifier

Another important mode of action of phytoestrogens is its epigenetic mechanisms. Epigenetics refers to molecular factors around DNA that regulate genomic activity independent of DNA sequence. The molecular factors involved are DNA methylation, histone modification, chromatin structure, and non-coding RNAs[22]. The binding of steroids and other ligands on hormonal receptors causes receptor dimerization. This leads to the recruitment of a co-activator or a co-repressor that is associated with Hormone-responsive elements, histone acetyl transferases and histone deacetylases. This mechanism leads to the transcription of genes regulated by hormones. The transcription machinery is regulated by a process called DNA methylation. DNA methylation and histone acetylation are the key players responsible for DNA repair, spoptosis, cell migration, proliferation, cell signalling and survival[23].

The epigenetic effects of flavonoids such as equol and coumesterol on a newborn mouse showed increased DNA methylation and resulted in the inactivation of a proto-oncogene H-ras[24]. DNA methylation patterns have been altered on treatment with a high dose of genistein on eight-week-old mice and genestein has a role in histone demethylation that can have a protective role in prostate cancer[25]. Recent studies show that phytoestrogens such as genestein and diadzein promote DNA demethylation in promotor regions of BRCA1, GSTP1, and EPHB2. Another study was carried out on PTEN's mRNA levels using semi-quantitative RT-PCR by stimulation of MCF-7 cells with quercetin, resveratrol and genestein resulting in increased PTEN protein levels[26]. This suggests that phytoestrogen stimulation even increases PTEN transcription[27]. Several *in vitro* studies on coumesterol and genestein have shown to decrease the methylation of a few tumour suppressor genes, which may be mediated by the inhibition of DNA methyl transferase activity[28]. Therefore this evidence suggests that phytoestrogens may allow silenced tumour suppressor genes to be re-expressed.

Other important factors that improve tumourogenecity are Hypermethylation of Histone Deacetylase (HDAC), Glutathione S-transferase 1 (GSTP1) and WNT5-a are also modified by phytoestrogens by de-methylation and inhibiting acetylation process. The various epigenetic mechanisms of phytoestrogens are tabulated in Table 1.

Table 1. Role of phytoestrogen in epigenetic modulation

Phytoestrogen	Mechanism	Promotor/Inhibitor	Therapeutic role
Genestein	Histone de methylation	Promotor	Breast cancer
Diadzein	DNA de methylation	Promotor	Breast/Prostate Cancer
Resveratrol	PTEN transcription P53 Acetylation	Promotor	Breast cancer/Prostate cancer
Coumesterol	DNA Methyl transferase (DNMT1)	Inhibitor	Breast Cancer
Genestein	Histone acetylation	Promotor	Breast/Ovarian cancer
Curcumin	DNMT1	Inhibitor	Breast Cancer
Curcumin	Hypomethylation	Promotor	ER+ Breast Cancer
Quercetin	DNMT1 HDAC1 H3 Acetylation	Inhibitor	Breast/Prostate Cancer
Catechins (EGCG)	Acetylation of Androgen receptor	Inhibitor	Prostate cancer
EGCG	de methylation (GSTP1)	Promotor	Prostate cancer
Naringenin	De methylation (WNT5a)	Promotor	Cervical cancer

3. Role of Phytoestrogens on Hormonal Cancer

3.1 Endometrial Cancer

Endometrial Cancer (EC) is the fourth most common cancer among women. 80-90 % of cases show a high incidence of endometrioid adenocarcinoma that is considered to be estrogen-dependent[29]. Studies suggest that the consumption of foods with high glycemic increased the risk of endometrial cancer whereas the intake of fruits and vegetables especially luteolin showed protective effects against EC and significant benefits in post-menopausal women. The metabolized products of phytoestrogens such as enterolactone prevent the formation of new blood vessels in EC and also promote cell death[30]. The intracellular estrogen signalling effects of soy isoflavones showed apoptotic effects in estrogen-dependent endometrial carcinomas. A study conducted on a mice model treated with resveratrol on induced endometriosis showed a decrease in vascular density and cell proliferation and improved apoptosis within the lesions[31]. In line with this studies carried out on Pueraria flower extract on human endometriotic and mesothelial cells showed inhibition of endometrial cell migration at 100µg/ml and also decreased the protein expression of Matrix metalloproteinase-9 (MMP-9) and Matrix metalloproteinase 2 (MMP2)[32]. Pueraria flower extracts are rich in genestein, puerarin and diadzein which contributed to the inhibitory potential. In addition, Naringenin increases apoptosis by acting on the stress regulatory genes on EC and activates MAPK signaling[33]. They also induce proapoptotic protein and suppressed cell proliferation by depolarization of mitochondrial membrane potential on VK2E6E7 and End1/E6E7 cell lines. A study accessed on the effect of resveratrol on endometrial stroma cells obtained from 40 endometriotic patients showed a reduction in the expression of IGF-1 and HGF and prevented cell proliferation through PI3K pathways[34]. Chyrisin, sylibinin, and quercetin also showed anti-proliferative properties on endometrial cancer[35].

3.2 Breast Cancer

Breast cancer is known to be the second leading cause of death among women. The expression of Estrogen Receptors (ER) such as ERα and ERβ has a critical role in breast cancer. ERα expression induces cell proliferation whereas ERβ is found to have protective effects on breast cancer[36].

The ERα receptor subtypes have an important role in cancer biology, tumour therapy and in gene regulation. The activation of ERα enhances cell proliferation and ERβ counteracts the effect of ERα mediated stimulation. ERα receptor is a unique steroid receptor as it interacts

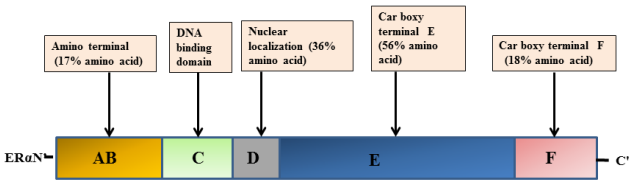

Figure 3. Structure of estrogen receptor alpha (Full length of estrogen receptor alpha contains 595 amino acids. The amino terminal comprises 17% amino acid. The receptor binding takes place in the D ring and the C ring contributes to DNA binding. The carboxy ring contains 56% of amino acid).

with many compounds. The receptor contains AB, C, D, E and F domains (Figure 3).

The AB terminal has a pincer-like arrangement that requires ligands to have an aromatic ring and the remaining binding pocket can accept many hydrophobic groups[37]. The overall interaction of ERα can be attributed to the binding cavity size. It has a volume almost twice that of the molecular volume of E_2. The length and width of the E_2 skeleton match the estrogen receptor. Studies show that several phytoestrogens such as genestein and coumestrol fit very well into the available space. Phytoestrogens contain aromatic rings with at least one hydroxyl group. Hydroxyl groups can be free and are mostly engaged in another function with an ester, ether or glycoside.

Selective Estrogen Receptor Modulators (SERMs) and Aromatase Inhibitors (AI) are the available synthetic treatments to treat hormone-dependent breast cancer which in a long run causes endometrial cancer and also leads to drug resistance[38]. The development of Musculoskeletal disorders is also frequently associated with AI treatment. Due to their structural similarity with estrogens, phytoestrogens can bind to ER receptor and exhibits antagonistic activity which in turn influences cell growth. In a study conducted on a breast cancer cell line treated with a combination of resveratrol and pterostilbene induced G2/M phase cell cycle arrest. This dual treatment with phytoestrogens downregulated the expression of Y-H2Ax and delayed early DNA damage responses which contributed to a preventive role in triple-negative breast cancer[39]. A prospective cohort study suggests that a high intake of soy-based food is associated with decreased risk of breast cancer[40]. In addition, heteronemin showed increased expression of ERβ mediated inhibition in MDA-MB231 cell lines and controlled proliferation of breast cancer cells[41]. Hesperidin was also found to have an inhibitory role on programmed cell death receptors and improved tumour immune response through AKT/NF-KB signaling[41]. A population-based cohort study done on Japanese women showed an inverse association between a high intake of fermented soy and breast cancer risk[42]. Hesperetin a metabolized product of hesperidin has down regulatory effects on cyclins in the G1 phase which attributes to cell cycle arrest in Breast cancer. Phytoestrogens such as genestein and quercetin are proven to induce cell proliferation in a dose-dependent manner. They also downregulate pi3k and AKT protein and induce apoptosis through the caspase pathway[43] (Figure 4).

3.3 Ovarian Cancer

Incidences of ovarian cancer are increasing at an alarming rate and it is considered to be lethal with a 30-40 % of survival rate[44]. 1 in 54 women is diagnosed with ovarian cancer in their lifetime[45]. Most of the women are diagnosed with advanced stages due to a lack of screening and prevention parameters. Aromatase Inhibitors (AI) are used in most gynaecological cancer including ovarian cancer. AI therapy is associated with side effects that lead to treatment discontinuation in most patients. Patients receiving AI experience musculoskeletal disorders[46]. There is a need to develop new strategies for the treatment of ovarian cancer. A study on the protection of phytoestrogens against ovarian cancer demonstrated with a combination of genestein and quercetin showed decreased proliferation in human ovarian carcinoma (OVCAR-5) cells[47]. Genistein and daidzein down-regulated the growth of two ovarian cancer cell lines, Caov-3 and NIH: OVCAR-3 *in vitro*[48]. In addition, genestein showed an anti-tumour effect against 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced rat ovarian carcinogenesis[49]. Another phytoestrogen coumestrol showed chemopreventive properties on ES_2 cells of ovarian cancer. They also inhibited the representative markers of ovarian cells such as PCNA and ERBB2 and controlled the proliferation of ovarian cells[50]. To know the effect of flax seeds on ovarian cancer, a study on hens fed with flax seed enriched diet was carried out. Flax seeds are rich in phytoestrogens and show anti-estrogenic effects. They reduced the expression of Cyclooxygenase enzymes and prostaglandin E_2 in ovaries[51].

3.4 Prostate Cancer

Prostate cancer is known to be the second most commonly diagnosed cancer among men. Prostate cancer is aggravated by androgen and thus the treatment aims to suppress the expression of androgens[52]. Androgen Deprivation Therapy (ADT) is considered to be the standard therapy in prostate cancer. The development of prostate cancer requires androgens as a key factor. They are present in the body as Testosterone and Dihydrotestosterone. ADT is associated with a decrease in testosterone levels through surgical treatments and with drugs such as Luteinizing Hormone Release Hormone (LHRH) agonists and antagonists, fatigue, musculoskeletal disorders and reduced bone mineral density. ADT in long term leads to osteoporosis and cardiovascular disorders[53]. Hence there is a need for multi-target therapy for the treatment of prostate cancer. A meta-analysis study on the association of phytoestrogen with prostate cancer concluded that genistein and glycetein are associated with a decrease in prostate cancer risk[54]. Another study showed Apigenin has beneficial effects on prostate cancer by down-regulating mRNA and protein expression in G_2 – M phase transition and inhibiting cell proliferation[55]. A clinical study carried out to know the effect of genestein on patients with localized prostate cancer showed that genestein promotes gene expression, DNA methylation and PTEN activation[56]. Another study on flaxseed-derived enterolactone showed anti-proliferative effects on prostate cancer in men[57]. In addition, luteolin acts as a potent agent against prostate cancer *in vitro* by inhibiting Anoctamin-1(ANO1) a chloride channel that is highly amplified in prostate cancer cells[58]. Resveratrol and quercetin also show chemopreventive properties against prostate cancer in both *in vitro* and *in vivo*[59].

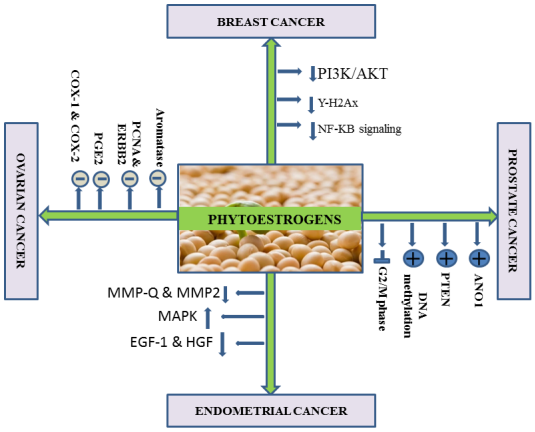

Figure 4. Various inhibitory mechanisms of phytoestrogens on hormonal cancer.

4. Conclusion

Based on the evidence from clinical studies and *in vitro* reports, It is evident that phytoestrogen exhibits beneficial effects on Reproductive cancers.

Most of the Case-control study reports conclude that the population with a high intake of phytoestrogens had a low risk of hormonal cancers. The metabolized form of phytoestrogens such as enterolactone had potent effects on controlling cell proliferation by interfering with various cellular signalling mechanisms. One such important role is the inhibition of kinases (MEK/MAPK) that plays a predominant role in cell migration and proliferation. Quercetin, Luteolin, Resveratrol and Diadzein exert their apoptotic potential by interfering with Cyclin-Dependent Kinases that are expressed in 50-60 % of breast cancers. They also downregulate PI3K an emerging target in most cancer diseases. Combination therapy of genestein and diadzein has an apoptotic role in ovarian carcinogenesis. Phytoestrogens also showed their inhibitory properties on Breast cancer and prostate cancer cell lines by downregulation of various nuclear enzymes such as FEN1, APE1, Topoisomerases and Aromatase. These enzymes have a multifunctional role in maintaining genome integrity and stability through the DNA repair process. Phytoestrogens such as Resveratrol, Genestein, Curcumin and Catechins Downregulate these key enzymes responsible for cell survival. Phytoestrogens are also involved in epigenetic alterations. Factors such as DNA hypermethylation and Histone Modification has a potential role in the transcription process. Thus it is speculated that phytoestrogens cause de-methylation and promotes the transcription of tumour suppressor genes such as PTEN, an important gene responsible for dephosphorylation. Phytoestrogens potentially inhibit reproductive tumours *in vitro* through mechanisms such as downregulation of mRNA and protein expressions, PIM1 inhibition, antagonising ER receptor, de methylation, inhibition of estrogen synthesis pathway and activation of transcription factors responsible for tumour suppression.

Pharmacokinetic and Pharmacodynamic profiling of phytoestrogens is less studied in malignancies. Safety profiling of individual phytoestrogens is required to extend their therapeutic property. Preclinical and clinical outcomes of phytoestrogen can be studied to identify potent inhibitors against reproductive tumours.

We conclude that phytoestrogens have multifunctional inhibitory potential on hormonal cancers. Genestein,

Resveratrol and Diadzein are often studied for their anti-cancer potential. Further research on other dietary estrogens and bioactive can be explored for hormonal cancers to improve their prevention and treatment options.

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