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The Dual Role of GPER in Triple-Negative Breast Cancer: Divergent Modulator of Tumor Progression and Suppression

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Abstract: Tripple negative breast cancer is the most aggressive kinds of breast cancer having ER negative, PR negative & HER2 negative leading to limited treatment option. Recent studies showed over expression of G protein – coupled estrogen Receptor in breast cancer cells. GPER is a membrane bound receptor mediate non-genomic signalling gathered attention for its complex role. GPER exhibit tumour promoting Properties through GFR – transactivation, PI3K/AKT, MAPK, CAMP, NFKB pathways leading to cancer. Development, proliferation, metastasis and epithelial mesenchymal transition (EMT). Likewise, GPER also having tumour suppressive role leading to caspase mediated apoptosis or cell cycle arrest in G2/M phase. GPER also inhibit proliferation, suppress EMT & reduce migratory potential suggesting a protective role against metastasis. Certain selective drugs of breast cancer like tamoxifen show resistance in GPER activated TNBC cells which cause GPER to be a potential target against breast cancer. This review explores along with mote dual role of GPER in TNBC, along with molecular mechanism & clinical approach of targeting GPER for therapeutic strategy challenging breast cancer subtypes.

Keywords: *Tripple Negative Breast Cancer (TNBC), G-Protein Coupled Estrogen Receptor (GPER), PI3K/AKT, MAPK, CAMP, NFKB, Epithelial Mesenchymal Transition (EMT).*

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I. INTRODUCTION

Breast cancer is the most common cancer ranking fourth in mortality. Estrogen mainly 17β- estradiol (E2) & its receptor is known to enhance the development & progression of cancer. GPER (G-protein Coupled estrogen receptor) also known as GPER 30, is a alternate estrogen receptor having seven transmembrane domain protein mediate rapid non-genomic response, is expressed in 50-60% of breast cancer tissue. Triple-Negative Breast Cancer (TNBC) is more aggressive kind of breast cancer lacking well defined receptor and signalling pathway but having prevalent GPER showing involvement in the growth of TNBC (Li – Han Hsu *et al.*, 2019). Certain selective estrogen modulator (SERM) like tamoxifen has been used to treat breast cancer cells but is found to be GPER agonist *(Gunter Emons et al.*, 2020*)*, which makes GPER an excellent target of breast cancer.

Contradictorily GPER has also shown pro-apoptotic function in Uveal melanoma cells by GPER agonist LN S8801 (Grazia Ambrosini *et al*., 2023) which made controversies regarding the proper functional role of GPER.

In this review dual role of GPER is examined on Breast Cancer Cells mainly TNBC & its pro- apoptotic effects. Certain drugs targeting GPER is also examined in this review for future epidemiology and laboratory studies.

II. ESTROGEN STRUCTURE, DISTRIBUTION AND SYNTHESIS

Estrogen, a primary female sex hormone, responsible for its function in female reproductive system as well as secondary sexual characteristics, belongs to the family of steroids, composed of 17 carbon-carbon bonds arranged as 4 fused sings (3 cyclohexane rings and a cyclopentane ring). Total 4 types of estrogen discovered: estrone, estradiol, estriol and estretrol having 18 Carbons ($C_{18}H_{24}O_2$) also

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known as C18 steroids, consist one benzene ring, a phenolic hydroxy group & ketone group in estrone or 1 in 17β estradiol, 2 in estriol & 3 in estretrol hydroxyl groups. (Nathalie Fuentes and Patricia Silveyra *et, al*, 2019)

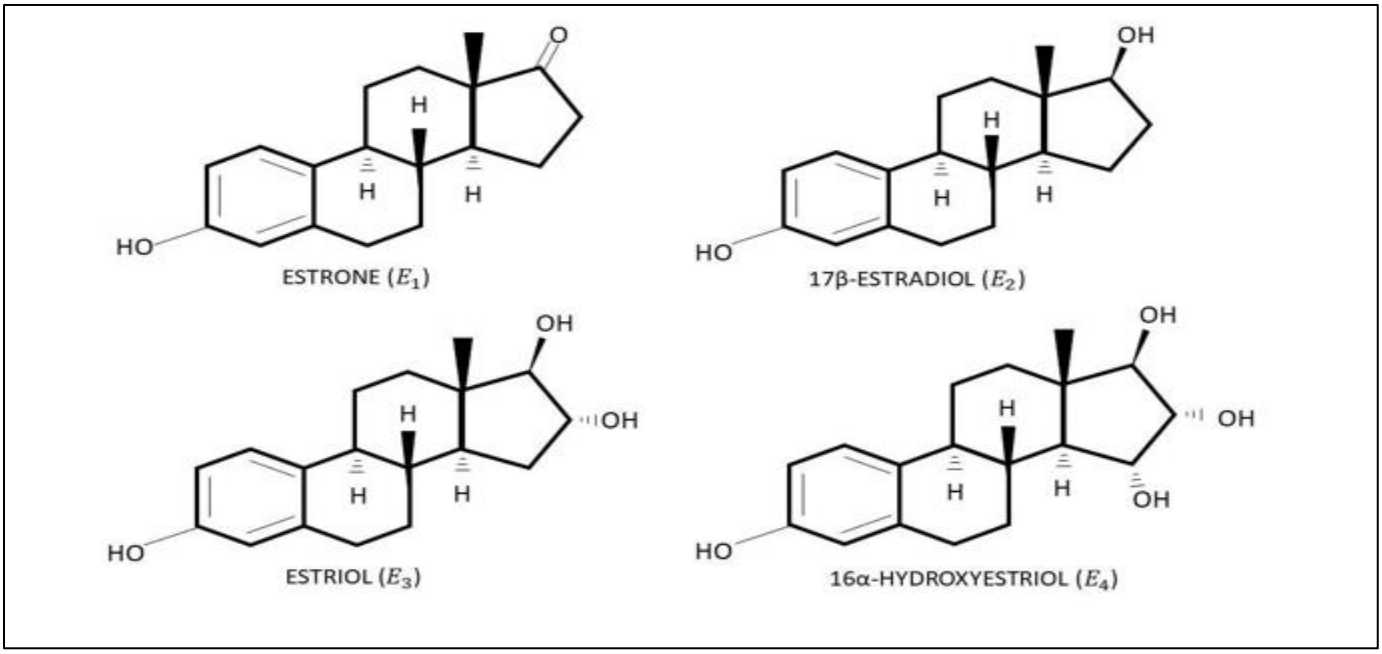

Fig 1 Chemical Structures of Endogenous Estrogens.
Estrone (E1), estradiol (E2), estriol (E3) and estretrol (E4).

Through primarily synthesized in ovary, estrogen is also synthesized in adrenal glands, adipose tissue (mesenchymal cells), including breast, osteoblasts, chondrocytes, aortic smooth muscle cells, Vascular endothelium, parts of brain and (extra gonadal tissues). Several studies have showed that estrogen level in post-menopausal women having breast cancer is higher in plasma. (Peter Vrtacnik *et al.*, 2014) Estriol & estretrol (15α–hydroxystriol) are predominantly found in Pregnant woman whereas estrone is found at higher levels in woman having menopause (Samavat & kurzer, 2015).

Cholesterol is the key initiator of estrogen biosynthesis. First cholesterol is translocated to inner mitochondrial (IMM) membrane a rate limiting step regulated by steroidogenic acute regulatory Proteins (STARD 1) acting as a shuttle enzyme. In IMM Cholesterol is converted to pregnolone by P450scc enzyme and then it acts as a precursor for all steroid hormones. Pregnolne diffusing through adjacent granulosa and theca cells of the ovary converts to androstenedione by enzyme CYP17A1 & 3B-HSD. Androstenedione is converted to estrone by CYP19A1 in granulosa cells. Estrone is converted to estradiol by 178B-HSD under the control of follicle Stimulating Hormone (FSH). (Nathalie Fuentes and Patricia Silverya, 2019)

Certain steroid C19 precursors like testosterone, androstenedione, dehydroepiandrosterone (DHEA) and dehydro-epiandrosterone sulfate (DHEAS) are essential for estrogen biosynthesis. Testosterone is first converted to 5α-dihydrotestosterone (DHT) and 17β –estradiol in target tissues. Similarly, DHEAS DHEA & androstenedione can also be converted to 17β estradiol or DHT through many enzymatic reactions. (Peter Vrtacnik *et al.*, 2014)

III. TYPES OF ESTROGEN RECEPTORS (ER)

Elwood Jensen in 1958 first discovered Estrogen receptors (ER) which can stimulate gene transcription after migrating to the nucleus. Two types of ER, ER & ERB highly homologous nuclear ERS (nERS) (Peng Chen *et al*., 2022*)* with three and five different isoforms respectively. It is examined that ERd and ERβ homodimers regulate different sets of gene from that of ERα/β heterodimer. Though having vast role of ERα in gene regulation it was suggested that ERβ exerts an inhibitory effect on Erα – mediated signalling. (Peter Vrtacnik *et al*., 2014).

➢ *Gper as a Novel Estrogen Receptor*

Another type of ER is G protein-coupled estrogen receptor (GPER1), a plasma membrane receptor also known as GPER 30 is identified through molecular cloning method, in 2012 (Nathalie Fuentes & Patricia Silveyra, 2019). GPER1 belongs to clan A (rhodopsin) family can translocate to the membrane of endoplasmic reticulum to exert different functions or to trans Golgi network to down regulation. (Yves Jacquot *et al*., 2021)

GPER is encoded in Chromosome 7 having 375 amino acids with molecular man 41 KDa, having Seven transmembrane α–helices & four extracellular Segments and four cytosolic segments, with weaker binding affinity to estrogen. (Peng Chen, *et al.*, 2022)

IV. MECHANISM OF ESTROGEN SIGNALING

There are Only 3 types of Estrogen signalling known till now, direct genomic signalling, Indirect genomic signalling and non-genomic signalling.

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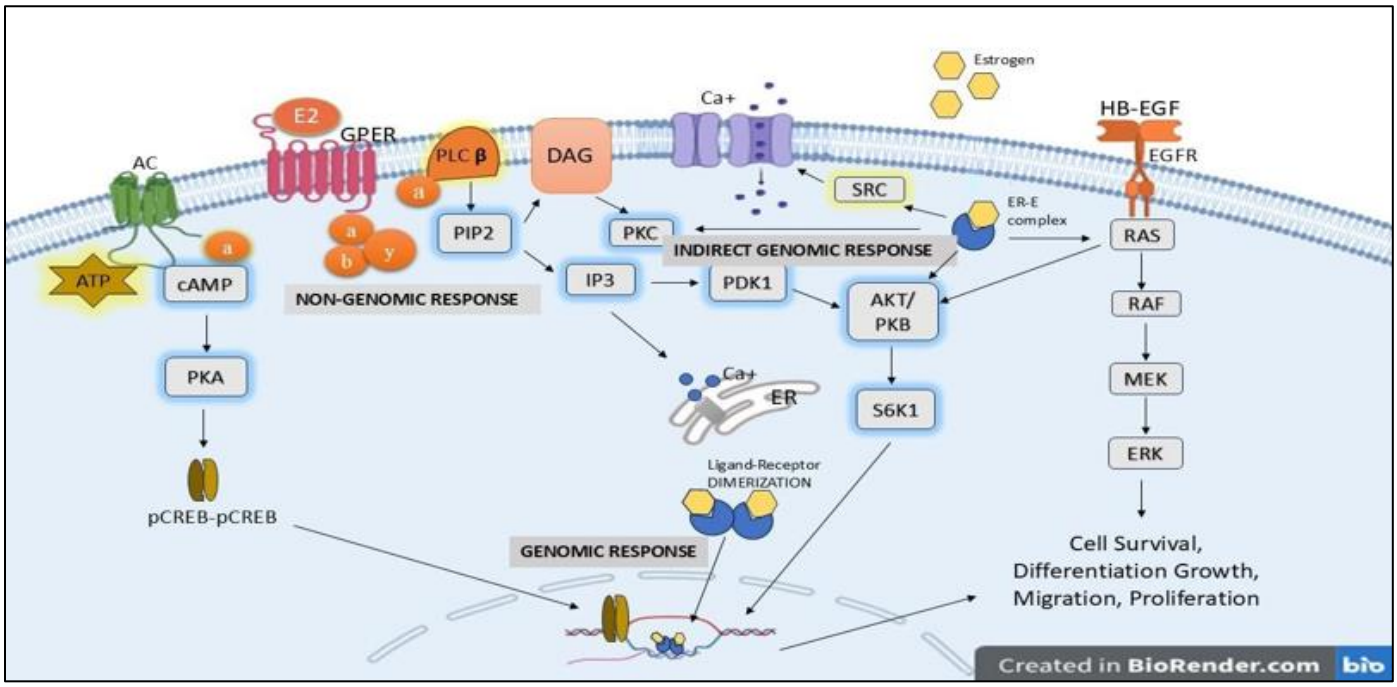

Fig 2 Estrogen Signals Through Three Main Pathways: Direct Genomic, Indirect Genomic and Non-Genomic

Figure2: Estrogen signals through three main pathways: Direct Genomic, where 17β- estradiol binds ERα/ERβ, leading to nuclear translocation and ERE-driven gene transcription; Indirect Genomic, involving ER interaction with other transcription factors without direct DNA binding; and Non-Genomic, where estrogen activates membrane-bound GPER1, triggering rapid signalling via pathways like PLC/IP3-DAG, cAMP/PKA, PI3K/Akt, MAPK, and EGFR.

Direct Genomic Signalling is known to be the classical mechanism of estrogen signalling occurs through binding of 17β-estradiol to ERα or ERβ in the cytoplasm of target cell, leading to a conformational change and receptor dimerization & ultimately translocation to the nucleus to bind with estrogen response elements (EREs) for transcription of target genes.

Indirect Genomic Signalling occurs without receptor ligand dimerization or directly binding to DNA but occurs through Protein-protein interaction with other classes of transcription factors by activating or repressing target gene expression.

Non-genomic Signalling occurs when estrogen binds with membrane bound GPER1 causing activation of various cell signalling pathways *(Peter Vrtacnik et al., 2014)* like activation of phospholipase C (PLC) / Protein kinase C throng 1P3 DAG Pathway or ion channels, or activation of Ca^{+} gated in channels or activating a denylate cyclase and increase Cyclic AMP/PKA in cell or signalling through phosphatidyl inositol 3 kinase (P13K) / Akt kinase pathways or promoting estrogen dependent activation of epidermal Growth factor (EGFR) *(Nathalic Fuentes and Patricia Silveyra, 2014).* Through this variety of a cascade signalling GPER activates nuclear transcription factors by opening in channels by Ca+ mobilization or activating pathways *(peng Chen et al., 2022)* like 1P3-DAG, CAMP, MAPK, Akt kinase the Ras-Raf etc. Long term estrogen activation is carcinogenic promoting inflammation and tumorigenesis. *(Chandra K. Maharanjan et al., 2022)*

V. ER IN BC (BREAST CANCER)

Breast cancer is the most common type of breast cancer affecting woman world and most commonly diagnosed cancer according to International Agency for Research in Cancers (GLOBOCAN) (Duo Zhang *et al*., 2012*)*. There are overall 3 types of breast cancers based on expression of ER, progesterone receptor (PR) and human epidermal growth factor 2 (HER 2). In Tripple Negative breast cancer all three are absent (ER^{-}, PR^{-}, $HER2^{-}$), whereas in HER2- positive breast cancer have (ER^{-}, PR^{-}, $HER2^{+}$) and lastly in Luminal A/B breast Cancer (ER^{+}, PR^{+}, $HER2^{-}$) is present. (Peng Chen, *et al*., 2022)

Estrogen plays a vital role in promoting breast cancer growth primarily by activating ERα which causes 70%. Of the breast cancer (Olive Treeck *et al*., 2020). ERα is overexpressed in 52 – 80% breast cancers tissues & only 10%. In healthy tissues which signifies role of ERα in promoting breast cancer (Peng Chen *et al*., 2022). Whereas ERβ tends to decrease during breast malignancy. Certain evidences suggest from in vivo & in vitro studies that ERβ have tumour suppressor properties causing suppression of growth & invasion of breast cancer cells. (Olive Treeck *et al*., 2020).

GPER1 play a vital role in breast cancer. Recent studies showed that GPER1 has been detected in 60% breast cancer tissue mostly in triple negative breast cancer (TNBC) and the combine effect of ERα & GPER1 is in about 40% of the breast cancer tissue (Olive Treeck *et al*., 2020*)*. Another cause of breast cancer is tumour microenvironment which promote carcinoma cells to transit from their epithelial nature to mesenchymal Characteristics called epithelial- mesenchymal transition (EMT). Estron, a GRER1 agonist Increases

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mesenchymal markers like vimentin & N-cadherin promoting EMT, tumour, progression and metastasis. (Lui's Molina Calistro *et al.,* 2025). So, downregulation of GPER 1 in tumour tissue is associated with poor survival (Peng Chen *et al*., 2022).

VI. ROLE OF GPER IN TNBC

The most aggressive kind of breast cancer having high mortality rate is Triple Negative Breast cancer (TNBC) that do not benefit from target therapies on ERAα. GPERI is majorly expressed in TNBC cells (Olive Treeck *et al*., 2020) which makes GPER a potential target. But there are certain controversies regarding the role of GPER in tumour promoting and tumour suppressive properties.

➢ *Tumor Promoting Effect*

In TNBC cells, GPER is overexpressed more than 68.8% upon binding with agonist and initiating progression of tumours. Overexpression of GPER is associated with metastasis tumour size HER 2/new and poor survival. GPER having diverse role in cell proliferation invasion, metastasis, angiogenesis modulation of cancer associated fibroblast (CAF), control of tumour stem cell functionality, cytokine production and secretion & invasion of Immune response. (Duo Zhang *et al*., 2024) In a study, GPER expression was overexpressed in metastasized breast cancer than primary tumours. GPER deficiency in mouse mammary gland tumour resulted in reduced tumour size & metastasis compared to wild type mice, in vivo (Eric R. Prossnitz and Matthias Barton, 2023). Palbocichib a cyclin D1- CDx 4/6 inhibitor, induces pro-inflammatory transcriptional events via GPER signalling in CAFs where GPER is found to contribute to reduce sensitivity to palbociclib resistance in breast cancer. (Marianna Talia *et al*., 2024). In another case study, GPER is found to be overexpressed in ER positive breast Carcinoma cell lines (MCF & T-47D and MDA-MB 361 where GPCR-Br was expressed in primary breast carcinoma cell lines and all 4 ER- positive tumour and on 1 of 7 ER-negative tumours (Charles Carmeci *et al*., 1997). Many cases show tumour promoting effect of GPER by knocking down GPER1. In a case Suggest that knockdown of GPER-1 in TNBC cells inhibited E2 induced proliferation, C–fos expression. Src kinase activation and EGFR transactivation, suggesting growth-promoting properties of GPER-1 in TNBC cells *(Oliver Treeck et al., 2020)*. Estrogen activated GPER1 causing FAK (focal adhesion kinas) phosphorylation in TNBC causing FAK inhibition and TNBC migration (Oliver Treeck *et al*., 2020). Contradictorily increased level of FAK is associated with TNBC as well as invasive & metastatic breast cancer (Duo Zhang *et al*., 2024*)*. Estrogen activated GPER-1 in MCF – 7 cells, through PI3x / Akt & ERK ½ signalling promotes cell proliferation, increases intracellular Ca^{2+} and reactive oxygen species (ROS). GPER and insulin like growth factor (IGFIR) association promote breast cancer metastasis proliferation & invasion modulating MAPK activation and EGFR signalling (Luis Molina Calistrol *et al*., 2025). In post- menopausal lymph node – negative patient absence of GPER predicted 91% disease free survival 73% in tamoxifen treated ER+ / PR+ GPER containing subgroup. GPER expression positively correlates with HER2 / neu tumour size & metastasis. (Li – Han Hsu *et al*., 2019). Estrogen activated GPER-1, Activating through ERK signalling causes increased cell growth, survival & invasion through upregulation of Cyclin A, cyclin DL Bcl-2 & C-fos expression, leading to cell cycle, anti-apoptosis, and proliferation respectively. GPER is found to be over expressed in TNBC cells lines MDA-MB-468, MDA-MD-436 (Li – Han Hsu *et al*., 2019*)*.

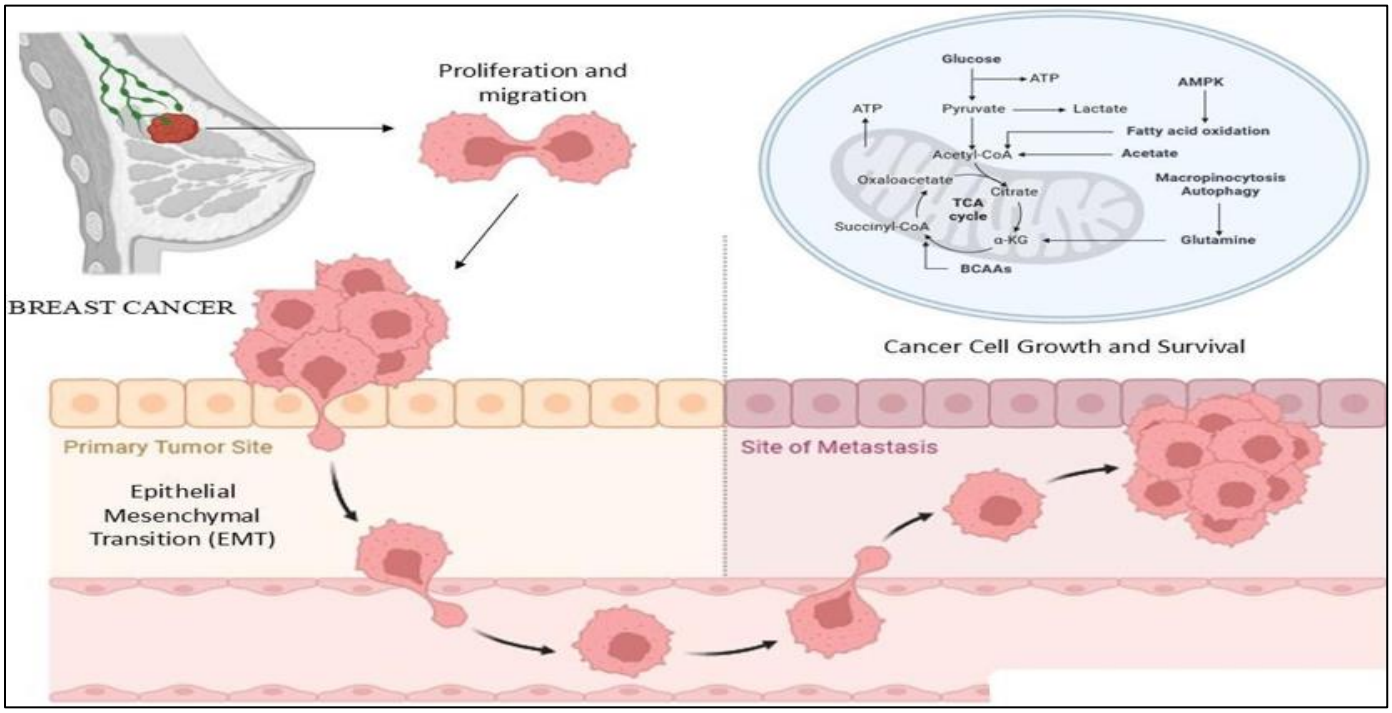

Fig 3 Schematic Illustration Showing Breast Cancer Progression, Highlighting Key Events Such as Uncontrolled Proliferation, Survival Signalling, Epithelial–Mesenchymal Transition (EMT), Invasion, and Metastasis.

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Table 1 Chart Showing Number of Papers Suggesting GPER to Cause Tumour Development, Migration and Metastasis:

Sl No.	Reference	Year	Key Findings	Tumour Effects
1.	Nicole A. Marjon	2015	In breast cancer cells, GPER increases tumour size, metastasis and reoccurrence in vivo	promoting
2.	Adele Vivacqua	2015	E2 activated GPER in SkBr3 breast cancer and HRpG2 hepatocarcinoma cells causes downregulation in Runx1 and upregulation in miR144 through PI3/ERK1/2/ELK1 pathway promoting cancer progression	promoting
3.	Sifeng Tao	2015	E2 binding GPER upregulated HOTAIR by suppressing miR148 leading to migration of breast cancer cells	promoting
4.	Adele Vivacqua	2018	17β-estradiol activated GPER in BR cells and carcinoma associated fibroblast (CAFs) show lower expression of miR-388-3p a potential inhibitor of cancer cell growth and invasion.	promoting
5.	Xiao-Sa-Li	2018	E2 activated GPER in ER^+ and ER^- BC cells cause FAK phosphorylation via GPER c-Src/ NF-kβ signaling promoting migration and invasion of cancer cells	promoting
6.	Sergio Liarte	2018	SIRT1 activates GPER in ER^+ BC cells causing cancer progression	promoting
7.	Kaihua Yang and Yufeng Yao	2019	In carcinoma associated fibroblast (CAFs) GPER expression is increased than normal fibroblast (NF). High GPER in CAF causes high expression of Coll1 to promote cancer proliferation, invasion and migration of cancer cells	promoting
8.	Francessca Cirillo	2019	3-methylcholanthrene (3MC) upon binding to aryl hydrocarbons (AHR) causes interaction with GPER to stimulate SkBr3 in BC cells and CAF cells.	promoting
9.	Luis Molina	2020	Tamoxifen treated MCF- BC cells cause over expression of GPER1 leading to cell proliferation.	promoting
10.	Adele Vivacqua	2021	E2/G1 activated GPER causes expression of certain miRNA which trigger tumorigenic effect in BC cells	promoting
11.	Huaicheng Yang	2021	E2 causes upregulation of GPER and downregulation of miR-124 in MCF-7 cells causing proliferation, invasion migration through miR124/CD 151 pathway	promoting
12.	Mariana Segovia-Mendoza	2022	17β-AEs upon binding GPER phosphorylate c-FOS, regulating proliferation of cervical and BC cells.	promoting
13.	Ana Carolina Tirado-Garibay	2023	GPER have several roles in promoting cancer development, metastasis and promoting epithelial mesenchymal transition (EMT).	promoting
14.	Liliana Torres-Lopez	2024	GPER is differentially expressed in healthy tissues and tumours of BC cells where GPER causes chemoresistance of multiple drugs.	promoting
15.	Segovia-Mendoza Mariana	2024	GPER having significant proinflammatory role by activating cytokines causing metastasis.	promoting
16.	Choungwu He	2024	Estrogen activated GPER in CAF upregulated GLUL and LDHB expression causing high glutamine production from TNBC cells promoting tumour progression through estrogen/GPER/Glutamine axis.	promoting

➢ *Mechanism of Signaling*

GPER 30/GPER, is a 7 transmembrane receptor, when activated by estradid in SKBR 3 breast cancer cells lacking nuclear ER activates cyclic AMP, inositol triphosphate (1P3) and Ca^{2+}, MAPK / ERK Pathways (Margarel A. Zimmerman *et al*., 2016)

E2. Activated GPER causes Ga subunit to activate adenyl cyclase to convert ATP into CAMP and GBy to subunit to activate SRC tyrosine kinase to activate α5β1 integrin and matrix metalloproteinase. (Marcelina E. Janik, et al., 2014). Heparin binding EGF growth factor is also activated and it stimulates EGFR transactivation by activating P13K/Ax+ & ERK ½ pathways. Transcriptionally activated GPER upregulated c-Fos., cyclin A, cyclin D1 and Connective tissue growth factor (CTGF), which causes breast cancers progression. GPER activation by estrogen also activates FAK (focal adhesion, kinase) to mediate cell proliferation and invasiveness and metastasis in TNBC. (Due Zhang, *et al*., 2024)

GIPER activated CAMP, PLC, Src proteins promotes

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MMP-2/9 activation resulting in EGFR transactivation & MAPK, ERK1/2; PI3K/Akt/mTOR & NFKB activation. Crosstalk between EGFR & insulin like growth factors 1 suggest carcinogenic mechanism (Naoko Honma *et al.*, 2021). Stimulation by G1 or EZ downregulates GPER regulated LncRNAs, enhancing glutamate transport & VGLUT2 expression by activating GPER-CAMP/PKA pathway to increase glutamate secretion & NMDA receptor signalling. CaMK & MEK / MAPK pathway boosts CREB phosphorylation promoting MMP7 transcription & contribute to TNBC invasion (Duo Z hang *et al.*, 2024) GPER causes endocrine resistance in BC cells by cross activation by tamoxifen (Richard A Peperras and Eric R. Prossnitz, 2020).

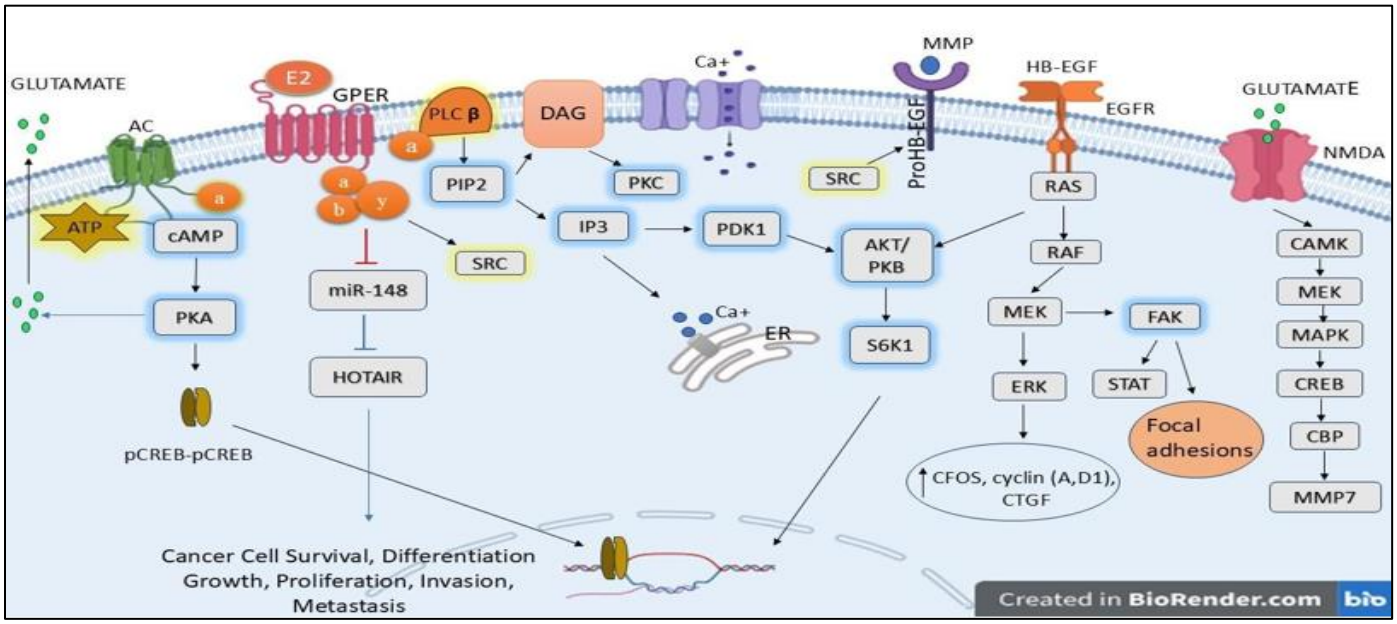

Fig 4 Mechanism of Action in GPER

Figure 4: Mechanism of action in GPER, a 7-transmembrane receptor, is activated by estradiol and signals via Gα (activating adenylate cyclase → cAMP) and Gβγ (activating Src kinase → integrins, MMPs). This leads to EGFR transactivation through PI3K/Akt and MAPK/ERK pathways. GPER also activates IP3/Ca^{2+}, PLC, FAK, and cAMP/PKA, promoting MMP7 transcription, glutamate secretion, CREB phosphorylation, and TNBC invasiveness.

➢ *Antitumor Properties*

Along with tumour promoting properties G.PER also possess antitumour properties. Some studies suggest that GPER agonist G1 inhibit TNBC via inducing cell cycle arrest in G-2/M phase causing H3 phosphorylation & Caspase 3 mediated apoptosis. (Oliver Treeck *et al*., 2020) Another study proved G1 as GPER agonist inhibit EMT & metastasis via down regulation of NE-KB signalling. (Duo Zhang *et al*., 2024) Other study suggested Gs triggering GPER inhibit interleukin 6 (1L-6) and Vascular endothelial cells (VEGF-A) leading to suppression of migration and angiogenesis in TNBC. E2 inducing by GPER also inhibit tumour growth by via reducing expression of VEGF-NF-B/P65, STAT and endothelial marker CD34 in TNBC cells (Oliver Treeck *et al*., 2020). Other studies suggest activated GPER downregulated NF-KB through phosphorylation of Gsk-3b by PI3K/Akt & ERK ½ leading to inhibition of EMT & metastasis (Zuo-Jia Chen *et al*., 2016). Cryptotanshinone (CPT) a major bioactive compound in Daushen known for its anti-inflammatory, antibacterial and antitumor properties activate GPER to inhibit proliferation in MCF-7 breast cancer cells by inducing G2 phase arrest and apoptosis (Danning shi *et al*., 2021).

ER-a36 receptor isoform in breast cancer cell lines inhibit TLR4/NF-kB signalling by interacting with GPER1 (George Notas *et al*., 2021) CPT by activating GPER-1 inhibit PI3K/AKT pathway in SKBR-3 cells showing antiproliferative properties (Danning Shi *et al*., 2020) 4-hydroxytamoxifen (4-0L+T) inhibits IGF-1 signalling in breast cancer cells through GPER1 and CREB mediated accumulation of extracellular IGFBP-1 (Ali Vaziri-Gohar and Kevin D. Houston, 2017). EZ activated GPER1 inhibit VEGF expression and angiogenesis in TNBC leading to tumour angiogenesis in TNBC cells. (Chens Wang *et al*., 2018), GPER activation inhibits proliferation migration invasion angiogenesis and EMT in MDA-MB 231 TNBC cells by upregulating E-cadherin and downregulating N-cadherin, Vimentin VEGFA, Angil and CD 151 (Ruiyan Huang *et al*., 2020). GPER specific activation inhibit breast cancer cell growth in concentration dependent manner by inducing cell cycle arrest at G2/M phase, increasing histone H3 phosphorylation and promoting caspase 3 mediated apoptosis (Christine Weibenborn et al., 2014). Estrogen receptor α derived peptide (ERα17p) exhibits antiproliferative, antiapoptotic, anti-inflammatory properties by activating GPER (Marilena Kampa et al., 2023). Chysin-loaded nanoparticles supress MDA-MB231 breast cancer cells by upregulating GPER expression and inhibiting MMPs and NF-kB (Kyoung Mec Kim et al., 2020). GPER activation by E4 upregulates SERPINB2 (a plasminogen activator type 2), mediating anti-inflammatory and anti-invasive effect in TNBC cells (Francessca Cirillo et al., 2024). Although GPER has demonstrated anticancer properties in ovarian cancer (Ignatov et al, 2013) and multiple myeloma (Maria Eugenia

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Gallo Cantafio et al., 2023), its direct antitumor role in triple-negative breast cancer (TNBC) remains inconclusive and requires further extensive research to be clearly established.

Table 2 Chart Showing Number of Papers Suggesting GPER to Cause Tumour Suppression:

Sl No.	Reference	Year	Key Findings	Tumour Effects
1.	Oliver Treeck	2020	GPER agonist G1 inhibit TNBC via inducing cell cycle arrest in G-2/M phase causing H3 phosphorylation & Caspase 3 mediated apoptosis	supressing
2.	Duo Zhang	2024	G1 as GPER agonist inhibit EMT & metastasis via down regulation of NF-KB signalling.	supressing
3.	Zuo-Jia Chen	2016	activated GPER downregulated NF-KB through phosphorylation of Gsk-3b by PI3K/Akt & ERK ½ leading to inhibition of EMT & metastasis	supressing
4.	Danning shi	2021	Cryptotanshinone (CPT) a major bioactive compound in Daushen known for its anti- inflammatory, antibacterial and antitumor properties activate GPER to inhibit proliferation in MCF-7 breast cancer cells by inducing G2 phase arrest and apoptosis	supressing
5.	George Notas	2021	ER-a36 receptor isoform in breast cancer cell lines inhibit TLR4/NF-kB signaling by interacting with GPER1	supressing
6.	Danning Shi	2020	CPT by activating GPER-1 inhibit PI3K/AKT pathway in SKBR-3 cells showing antiproliferative properties	supressing
7.	Ali Vaziri-Gohar and Kevin D. Houston	2017	4-hydroxytamoxifen (4-0L+T) inhibits IGF-1 signalling in breast cancer cells through GPER1 and CREB mediated accumulation of extracellular IGFBP-1	supressing
8.	Chens Wang	2018	EZ activated GPER1 inhibit VEGF expression and angiogenesis in TNBC leading to tumour angiogenesis in TNBC cells	supressing
9.	Ruiyan Huang	2020	GPER activation inhibits proliferation migration invasion angiogenesis and EMT in MDA-MB 231 TNBC cells by upregulating E- cadherin and downregulating N-cadherin, Vimentin VEGFA, Angil and CD 151	supressing
10.	Christine Weibenborn	2014	GPER specific activation inhibit breast cancer cell growth in concentration dependent manner by inducing cell cycle arrest at G2/M phase, increasing histone H3 phosphorylation and promoting caspase 3 mediated apoptosis	supressing
11.	Marilena Kampa	2023	Estrogen receptor α derived peptide (ERα17p) exhibits antiproliferative, antiapoptotic, anti- inflammatory properties by activating GPER	supressing
12.	Kyoung Mec Kim	2020	Chysin-loaded nanoparticles supress MDA- MB231 breast cancer cells by upregulating GPER expression and inhibiting MMPs and NF-kB	supressing
13.	Francessca Cirillo	2024	GPER activation by E4 upregulates SERPINB2 (a plasminogen activator type 2), mediating anti-inflammatory and anti-invasive effect in TNBC cells	supressing

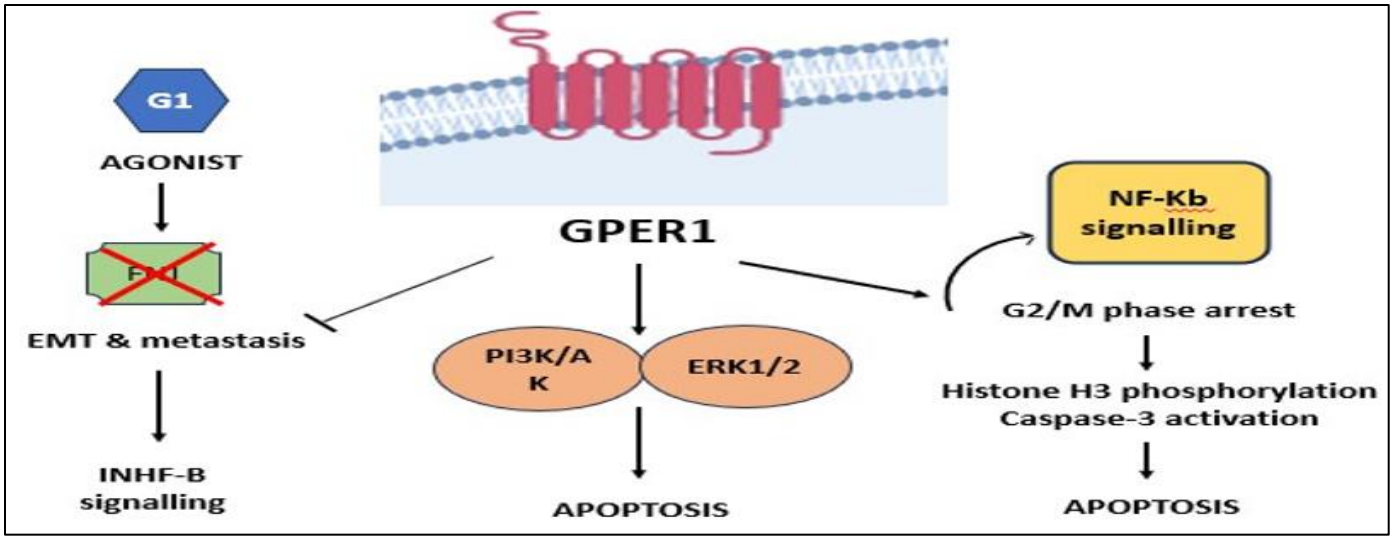

Fig 5 Tumour Suppressive Role of GPER: GPER Agonist G1 Inhibit TNBC via Inducing Cell Cycle Arrest in G-2/M Phase Causing H3 Phosphorylation & Caspase 3 Mediated Apoptosis

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VII. TARGET DRUGS

GPER have complex signalling process with growth promoting factors in TNBC cells along with migration, EMT. So, targeting GPER with certain drugs would be beneficial in TNBC patients. Certain treatments which block estrogen biosynthesis prevents Er & GPER action (Milad Rouhimoghadam *et al*., 2020). Role of GPER in cancer promoting ways Can also a reason for developing GPER targeted cancer therapeutics to suppress tumour (Keith A. Hall and Edward J. Filardo, 2023) Certain selective estrogen modulator like Tamoxifen is used to treat certain breast cancer cells (Gunter Emons *et al*., 2020). E2 signalling via tamoxifen (TAM) or aromatase inhibitors is a significant therapeutic approach for the treatment or prevention of estrogen receptor (ER) positive breast cancer. (Milena Rondon-Lagos *et al*., 2016). So, Tamoxifen is a potent drug to treat hormone dependent breast cancer and most frequently prescribed anticancer drugs world-wide (Gunter Emons *et al*., 2020). But certain studies confirmed that GPER signalling contributes to tamoxifen (7AM) resistance involving bidirectional crosstalk with 11GFs (Veranica Vella *et al*., 2020), Certain studies confirmed that casein kinase 1 (CK1) using CK1-7 and 1C261 Blocks 4- OHT induced ERα activation EGFR translocation and GPER 1/Src signalling in Ishikawa cells suppressing endometrial carcinogenesis which suggests that CK1 can be a promising adjacent strategy for breast cancer patients undergoing tamoxifen therapy (Long Ngo Hoang and Sook-Jeong Lee, 2022) Long term. Tamoxifen use causes drug resistance due to downregulation of ERα expression and abnormal activation of P13K/AKT/mTOR signalling pathway. So certain approach like methylation for tamoxifen is used to recover the resistance to tamoxifen (Jin Shen *et al*., 2024). Salvia miltiorrhiza (Danshen) component tanshinone IIA (Tan IIA) shows anticancer effects by binding strongly to GPER, reduces GPER, EGFR, ERK, c-Fos, and c-Jun expression, inhibits proliferation and migration, and induced apoptosis, highlighting GPER as a potential therapeutic target in TNBC (Yushuang he et al., 2023).

VIII. DISCUSSION

GPER having dual role in tumour progression and tumour resistance. On meta-analysis in PubMed, Google Scholar and Research Gate, searching 'GPER tumour suppression', 90 papers were suggested out of them. 16 papers suggest tumour suppressive role of GPER in breast cancer and on searching "GPER tumour progression", about 150 papers were suggested. Though many paper suggested regarding anti-tumour effect of GPER but still there are some controversies due to limited papers. Certain drugs targeting GPER played vital role in tumour suppression. Other drugs like tamoxifen cause tumour suppression in ER- positive breast cancer cells but long-term use causes drug resistance, which is again used as methylated tamoxifen to suppress drug resistance. Certain bioactive compounds like CPT having anti- inflammatory & anti-tumour properties activate GPER to inhibit proliferation in MCF-7 breast cancer cells inducing G2 phase arrest and apoptosis.

IX. CONCLUSION

Considering all factors GPER plays dual role in tumour suppression and tumour promoting mechanism in breast cancer cells mainly is TNBC. Although its direct antitumor role in triple- negative breast cancer (TNBC) remains inconclusive and requires further extensive research to be clearly established. GPER also have treatment resistance and tumour growth properties in ERα positive subtypes. Targeting GPER and its downstream signalling is a unique treatment approach for ERα negative and positive breast cancer cells. To maximize therapeutic results, future treatments should take into account regarding GPER-selective modulators & ERα- specific antagonists, lacking GPER action.

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