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Review

The onus of cannabinoids in interrupting the molecular odyssey of breast cancer: A critical perspective on UPR^{ER} and beyond

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ABSTRACT

Cannabinoids, commonly used for medicinal and recreational purposes, consist of various complex hydrophobic molecules obtained from *Cannabis sativa* L. Acting as an inhibitory molecule; they have been investigated for their antineoplastic effect in various breast tumor models. Lately, it was found that cannabinoid treatment not only stimulates autophagy-mediated apoptotic death of tumor cells through unfolded protein response (UPR^{ER}) activated downstream effectors, but also imposes cell cycle arrest. The exploitation of UPR^{ER} tumors as such is believed to be a major molecular event and is therefore employed in understanding the development and progression of breast tumor. Simultaneously, the data on clinical trials following administration of cannabinoid is currently being explored to find its role not only in palliation but also in the treatment of breast cancer. The present study summarizes new achievements in understanding the extent of therapeutic progress and highlights recent developments in cannabinoid biology towards achieving a better cure of breast cancer through the exploitation of different cannabinoids.

Contents

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1. Introduction

The preparations from *Cannabis sativa* L. (marijuana) hold a strong foothold in the history of mankind, where it is registered to have usage both in recreational as well as medicinal activities. Encompassing a family of complex hydrophobic molecules, preparation from *Cannabis sativa* L. binds and as such activates cognate cannabinoid receptors (which are G-protein coupled receptors, GPCR) in mammalian systems, (Matsuda et al., 1990). These endogenous arachidonic acid derived receptors encouraged scientific community to delineate the existence of an endocannabinoid ligand receptor system in mammals (Bisogno et al., 2005). In addition to two major cannabinoid receptors (CBRs; CB1 and CB2) that show spatial expression pattern, transient receptor potential vanilloid 1 (TRPV1) and G-protein coupled receptor 55 (GPR55) are also reported to bind endocannabinoids (Pertwee et al., 2010). CB1 being ubiquitous, not only shows high-density expression pattern in the central nervous system (known for translating psychoactive effects), but is also found in peripheral neurons, testis, uterus, adipocytes etc. (Devane et al., 1992; Mackie, 2005). The distribution of CB2 dominates mainly in the immune system (Pertwee et al., 2010). The cognate cannabinoid ligands for the existing receptors categorically fall into three groups: (i) endocannabinoids (ii) phyto-cannabinoids and (iii) synthetic analogues (Di Marzo and Petrocellis, 2006). Anandamide (Devane et al., 1992) and 2-arachidonoyl glycerol (2-AG) (Mechoulam et al., 1995), being the most studied endocannabinoids are involved in a wide array of regulatory roles in the living system (Katona and Freund, 2008; Pertwee, 2009b).

Of the 108 *C. sativa* derived phyto-cannabinoids, Δ^9-tetrahydrocannabinol (THC) is the most active and abundant psychoactive cannabinoid (Diviant et al., 2018; Micale and Drago, 2018). Subjected to a multitude of studies, THC was found to exhibit therapeutic effect against cancer (Pertwee, 2008; Pokrywka et al., 2016; Scott et al., 2017). Another phyto-cannabinoid of notable interest is cannabidiol (CBD) that has also been found to inhibit the functionality of cancer cells (Lanza Cariccio et al., 2018; Scott et al., 2017; Shrivastava et al., 2011). Compared to natural ones, the synthetic agonists for cannabinoid receptors; WIN55, 212-2 and JWH-133 have also been shown to exert dose-dependent anti-proliferative effect on breast cancer cells (Emery et al., 2014; Qamri et al., 2009). Additionally, anandamide and CBD are also found to exhibit CB receptor independent actions (Patsos et al., 2005). Although, comprehensive repertoire exists that inarguably decipher the role of CB agonists in inhibiting cancer in preclinical studies (De Petrocellis et al., 1998; Gomez del Pulgar et al., 2002; Guzmán et al., 2001; Sanchez et al., 2001), the therapeutic potential of cannabinoids in clinics is restricted to palliative care of cancer patients (Caffarel et al., 2012). There are numerous studies performed on different models of breast cancer studies where cannabinoids have been used to challenge tumor proliferation and metastasis. The present study unfolds an attempt to highlight the involvement of stress stimuli, the endoplasmic reticulum stress (ERS) hence the endoplasmic reticulum unfolded protein response (UPR^{ER}) showing the antineoplastic effect of cannabinoid in breast malignancy.

2. Cannabinoid receptor signaling

The canonical pathway that mediates the signaling of cannabinoid receptors CB1/CB2 starts with the binding of cannabinoids. The step is followed by coupling of $G_{i/0}$ proteins to CBRs, where α_i subunit inhibits adenylyl cyclase (AC) and hence synthesis of cAMP. This diminishes the concentration of protein kinase A (PKA) but increases the activity of potassium channels type A due to which hyperpolarization of the membrane results. Another subunit, α_0, inhibits the voltage-dependent Ca^{2+} channels, displaying an overall impediment of membrane depolarization. Additionally, β_γ subunit associates with signaling molecules like phosphoinositol 3-kinase (PI3K) or protein kinase B (PKB/Akt). Cannabinoid treatment also activates the enzyme, neutral sphingomyelinase, which is coupled to the CBRs, mediating the production of ceramide that acts as second messenger participating in various signaling pathways as described elsewhere (Fernandez-Lopez et al., 2013).

The cannabinoid receptors (CB1/CB2) naturally found in abundance in neurons, specifically the presynaptic neuron, take part in retrograde modulation. The release of neurotransmitters (Glutamate) from the presynaptic neuron activates the influx of Ca^{2+} (leading to increase in Ca^{2+} concentrations) in postsynaptic neuron after binding of the neurotransmitters to their cognate postsynaptic receptor. This event initiates endocannabinoids biosynthesis: glycerophospholipid combines with phosphatidylethanolamine in the presence of *N*-acyltransferase (NAT) to give *N*-arachidonoyl-phosphatidyl-ethanolamine, which is acted upon by *N*-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD) to give anandamide; on the other hand glycerophospholipid is acted upon by phospholipase C (PLC) to give *sn*-1-Acyl-2-arachidonyl glycerol that gives 2-AG under the enzymatic activity of *sn*-1-selective diacylglycerol lipases (DAGLs) (Di Marzo et al., 2004). The released anandamide and/or 2-AG from the postsynaptic neuron migrate in a retrograde modulatory way to bind to their cognate CB1/CB2 receptors on the presynaptic neurons leading to regulation of ion channels. This results in the inhibition of further neurotransmitters release via lowering of the Ca^{2+} influx in presynaptic neuron (Ahn et al., 2008). The system of cannabinoid action is described in Fig. 1.

3. Receptor profiling in breast cancer

Breast cancer shows intra-tumor heterogeneity at molecular, genomic and phenotypic levels, where tumor development is fueled by a battery of molecular anomalies that results in diverse clinical consequences. Molecular stratification of breast cancer based on the receptor status is the most reliable way used in the prognosis, prediction and treatment response of patients. Study of the expression levels of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki-67 are exploited in the molecular subtype classification of breast cancer, which is described as- Luminal A: positive for ER and/or PR, negative for HER2 and Ki-67 low; Luminal B: positive for ER and/or PR, negative for HER2 and Ki-67 high; HER2 enriched: negative for ER and PR, positive for HER2, and Triple-negative

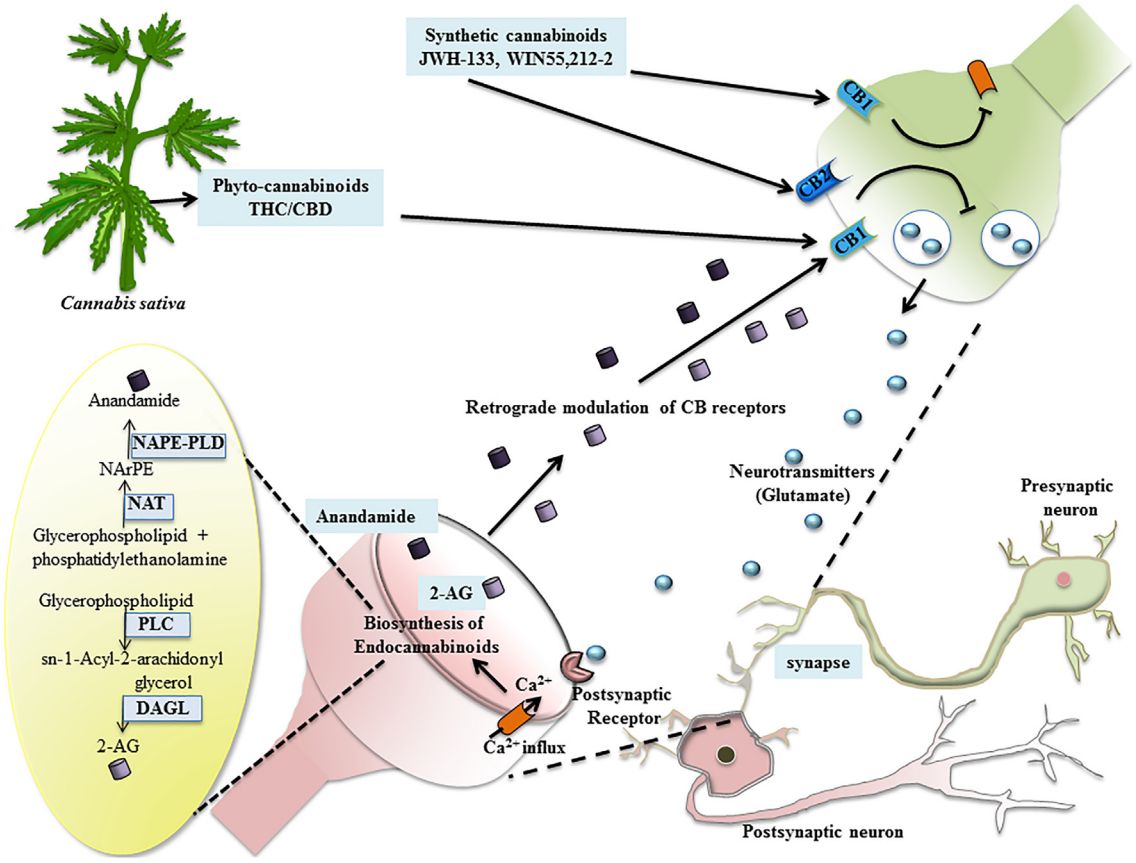

Fig. 1. The system of endocannabinoid and cannabinoids. The cannabinoid receptors (CB1/CB2) naturally found in abundance in neurons, specifically the presynaptic neuron, take part in retrograde modulation.

breast cancer (TNBC): negative for ER, PR and HER2 (Dai et al., 2015; Hon et al., 2016). Another extensively discussed subtype is the basal-like breast cancer (Badve et al., 2011).

The expression pattern of CB1 and CB2 receptors vary among breast cancer subtypes. CB1 is detected in 28% of breast carcinomas, with preponderance in HER2 tumors (14%), whereas CB2 shows in 72% of breast tumors where it is again expressed predominantly in HER2 sub-type (91%). WIN-55 and 212–2 mediated activation of CB1 and/or CB2 receptors in TNBC xenografts has been shown to significantly diminish the growth and metastasis of tumor (Qamri et al., 2009). In two separate studies, CBD and THC both were shown to hinder the growth and metastasis of tumor in TNBC xenograft and HER2 positive (MMTV-neu mice as well as xenograft mice) respectively (Caffarel et al., 2010; Murase et al., 2014). The data on *in vivo* HER2 positive and TNBC model studies implicate the anti-tumorigenic action of phyto-cannabinoids, endocannabinoids and synthetic cannabinoids.

The expression pattern of CB receptors and prognosis of various breast malignancy subtypes shows an association. The anti-proliferative effect of anandamide in ER^+/PR^+ breast cancer cells has been proven to be through the activation of CB1 receptors (De Petrocellis et al., 1998; Melck et al., 1999; Melck et al., 2000). Studies on the activation of CB2 receptors through JWH-015 agonist in luminal-A breast cancer cell lines, MCF7 cells; showed impediment in migration and invasion (Nasser et al., 2011). HER2 tumors, which give poor response to conventional cancer therapy, showed higher expression levels of CB2 (Guzman, 2003). In basal-like and TNBC cell line, MDA-MB-231 and xenograft- based model, cannabinoid treatment targeted CB1 showed the inhibition of cell proliferation (Laezza et al., 2006; Qamri et al., 2009). A novel study elucidated the anti-proliferative and cell invasion impeding actions of CBD in the metastatic cell line, MDA-MB436 (McAllister et al., 2007). GRP55 is activated by two agonists, lysophosphatidylinositol (LPI) (Oka et al., 2010) and anandamide (Lauckner et al., 2008). A report suggests that LPI-GRP55 axis is important in the modulation of migration and orientation of MDA-MB231 and MCF7 cells (Ford et al., 2010). Also in basal-like and TNBC breast cancer cells, surge in the expression of GRP55 complements higher metastasis and poor patient prognosis (Andradas et al., 2016). Furthermore, the hetero-dimerization complex of CB2-GRP55 in luminal B type, BT-474 cells display critical tumor growth control response to THC treatment (Moreno et al., 2014). Elbaz et al, have validated the molecular mechanism of CBD action in TNBC cell line wherein CBD inhibited epidermal growth factor (EGF) induced tumor characteristics (Elbaz et al., 2015). Another study delineated the CBD molecular course of action in MDA-MB231 cell lines (McAllister et al., 2011).

4. ERS induced UPR^{ER} and its consequences in breast cancer

Metastasis is a notable cause of mortality in breast cancer patient where the progressing tumor pursues admittance to vascular and lymphatic systems (Friedl et al., 2012; Hanahan and Weinberg, 2011). Breast malignancy is a solid tumor that characteristically shows hypoxia and nutrient deprivation (Nagelkerke et al., 2013). Hypoxic conditions are known to induce UPR and the later has been shown to stimulate cell-cycle arrest (Bourougaa et al., 2010). The stressful conditions arising during tumor proliferation, puts special demand on cellular microenviron-

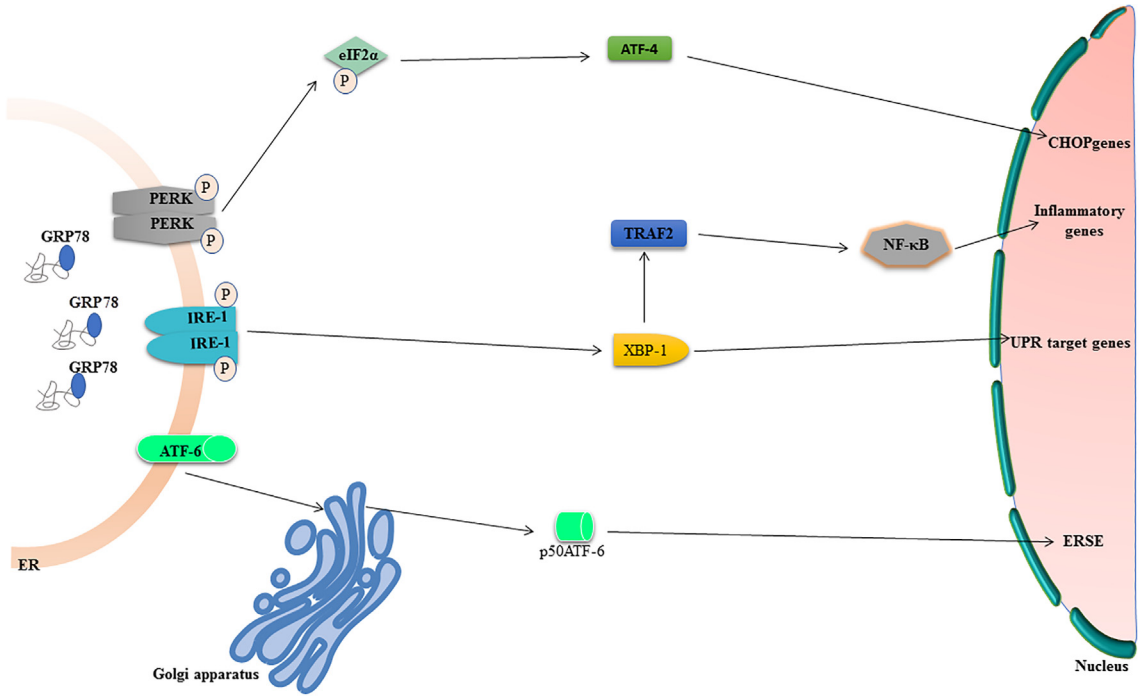

Fig. 2. Molecular mechanism of ERS induced UPR^{ER}. Under the imposed stress, GRP78 is recruited to client misfolded peptides, thereby freeing the luminal domains of UPR^{ER} sensors, PERK, IRE1α and ATF; marking their activation through a series of events.

ment for higher rates of transcription as well as translation, thereby resulting in ERS (Yadav et al., 2014); which has been documented to trigger growth arrest in the melanoma cells (Han et al., 2013).

The progressing breast tumors exert elevated requirement on cellular translation for their proliferation. ER is burdened with nascent peptide synthesis, which overshoots the folding capacity of ER luminal molecular chaperones like GRP78 (78 kDa glucose-regulated protein) etc. This causes the accumulation of unfolded/misfolded peptide cargo in the ER lumen. The ensuing ERS triggers UPR^{ER}, aimed at rescuing the cellular microenvironment through a series of the transcriptional ensemble. The normal physiology of breast during the menstrual cycle responds to hormonal stimulus, whereby it establishes UPR^{ER} for maintaining proteostasis. However, progressively higher cellular demand of breast tumors chronically imposes the stress; thereby reinstating UPR^{ER}, which consequently favors cellular immortality (Minakshi et al., 2017).

4.1. Molecular mechanism of ERS induced UPR^{ER}

The molecular sensors of UPR^{ER} are the three ER transmembrane proteins: PKR-like ER kinase (PERK), inositol-requiring protein 1α (IRE1α) and activating transcription factor 6 (ATF6). GRP78 holds a dynamic balance between its peptide folding job and being held with the intra-luminal domains of UPR^{ER} sensors. Under the imposed stress, GRP78 is recruited to client misfolded peptides, thereby freeing the luminal domains of UPR^{ER} sensors marking their activation through a series of events (Fig. 2).

GRP78 overexpression has been reported in breast malignancy (Yao et al., 2015). In a study on basal-like subtype breast cancer transgenic mice (MMTV-PyVT) model, GRP78 has been proven to be critical for tumor proliferation, survival and angiogenesis (Dong et al., 2008). PERK and IRE1α, both undergo homodimerization and trans-autophosphorylation (p-PERK and p-IRE1α respectively). p-PERK phosphorylates cytosolic eukaryotic initiation factor 2α (eIF2α) causing attenuation of global translation and selective translation of mRNAs with internal ribosome entry site (IRES) like GRP78 and activating transcription factor 4 (ATF4). ATF4 upregulates a compendium of genes involved not only in amino acid biosynthesis and antioxidant response, but also in the late expression of C/EBP homologous protein (CHOP) that promotes apoptosis (Rahman et al., 2018). In highly deprived breast tumor microenvironment, the PERK signaling has been well documented in the MMTV mice model wherein PERK/CHOP/ATF4 arm potentiates tumor progression (Bobrovnikova-Marjon et al., 2010).

p-IRE1α has an active kinase and endoribonuclease domain that results in the non-canonical splicing of X-box binding protein 1 (XBP1) mRNA. The spliced XBP1 (s-XBP1) gives XBP1 transcription factor that upregulates genes involved in protein folding, expansion of the ER compartment and ER-associated protein degradation (ERAD). The treatment of MCF7 cells with 17β-estradiol (E2) has been shown to precisely upregulate XBP1 (Wang et al., 2004). Additionally, measurable levels of s-XBP1 were detected in luminal as well as basal-like breast cancer cell lines, where s-XBP1 supported tumorigenicity and recurrence of TNBC (Chen et al., 2014). Conversely, p-IRE1e also activates TNF receptor-associated factor 2 apoptosis signal-regulating kinase1 (ASK1-TRAF2), which leads to JNK phosphorylation that engages in apoptosis (Minakshi et al., 2017; Rahman et al., 2017). IRE1 intersects with inflammatory response where the key inflammatory modulator, NF-κB, is activated by IRE1-TRAF2 complex (Hu et al., 2006). In studies on anti-estrogen-resistant MCF7 cells, s-XBP1 has been shown to upregulate NF-κB leading to antiestrogen resistance (Hu et al., 2015).

In a parallel set of events, ATF6 (90 kDa protein), gets translocated to the golgi membrane after dissociating from GRP78, whereby it undergoes cleavage by the action of serine proteases; Site-1 protease (S1P) and Site-2 protease (S2P). The functional isoform of ATF6 thus released from golgi is 50 kDa (p50ATF6) fragment that is a transcription factor acting in cis on ER stress response elements (ERSE). p50ATF6 also targets upregulation of genes for ER chaperones (GRP78) and CHOP (Wu et al., 2007). Anal-

ysis of the effect of overexpression of active ATF6 shows that it mediates apoptosis in C2C12 (a mouse skeletal muscle cell line) cells but not in MCF7 cells (Morishima et al., 2011).

The activation of CHOP further stimulates the expression of pro-apoptotic proteins like growth arrest and DNA damage-inducible protein 34 (GADD34) and tribbles-related protein3 (TRB3). Pro-apoptotic proteins from BCL2 family, BAX/BAD, also get upregulated by CHOP (Minakshi et al., 2017). Data represented by Kato et al., discloses the apoptotic role of IRE1-JNK induction through Akt/mTOR/PI3K axis (Kato et al., 2012; Qu and Shen, 2015). Experimental data on breast cancer cell lines further establish the participation of Akt/mTOR and IRE1/JNK alliances in cell death (Park et al., 2016).

In a recent study by Dai et al., the BRCA1 associated protein 1 (BAP1), a tumor suppressor, has been shown to be pro-survival (Dai et al., 2017). Albeit, BAP1, which is seldom mutated in breast cancer, promotes breast malignancies. Also in BAP1 knockdown systems observation of significant decline in breast lung metastasis has been registered (Goldstein, 2011; Qin et al., 2015). The mechanistic details of BAP1 induced repression of UPR^{ER} mediated cell death presents an interesting scenario of contradictions (Qin et al., 2015). So, it's reasonable here to think about the anticipatory role of cannabinoids, where it induces ERS UPR^{ER} that can interfere BAP1 signaling thereby checking proliferation of tumor. In one of the classical studies, anandamide treatment of EFM-19 cells showed measurable diminished concentration of *brca1* protein (De Petrocellis et al., 1998). Conversely, GRP78 has been shown to be an effector of BRCA1 that prevents ERS-induced apoptosis in MCF7 cells (Yeung et al., 2008).

In malignant breast tumors, the higher expression level of GRP78 (a marker of UPR^{ER}) has been linked with the development of chemotherapy resistance (Cook and Clarke, 2015). The cell surface localization of GRP78 (not found in normal cells) has also been associated with inhibition of apoptosis leading to the immortality of tumor (Tsai et al., 2015). Excitingly, the translocation of GRP78 is concomitant with the cell surface localization of Par-4 (Prostate apoptosis response-4, a pro-apoptotic protein) resulting in the deputation of extrinsic apoptotic pathway (Burikhanov et al., 2009). One remarkable study on osteosarcoma MG63 cells, described that WIN 55, 212-2-treated cells showed concomitant rise in cell surface localization of Par-4/GRP78 complex as opposed to normal cells and subsequently enhanced autophagy-mediated apoptosis through UPR^{ER} activation (Notaro et al., 2014). This remarkable study can be simulated in breast cancer models to look for similar findings.

5. Impact of cannabinoids on UPR^{ER}

Studies advocate the induction of autophagy and inhibition of cell-cycle progression in breast tumor after cannabinoid treatment. Here we discuss various mechanistic details of UPR^{ER} activated downstream effectors after undergoing cannabinoid treatment.

5.1. de novo ceramide synthesis

Ceramide, a second messenger sphingolipid present in plasma membrane, actively regulates various cellular processes including apoptosis (Hannun, 1996). The *de novo* synthesis of ceramide in ER lumen elicits ERS in the tumor followed by UPR^{ER} after cannabinoid treatment. Ceramide executes the formation of reactive oxygen species (ROS) that results in an incessant oxidative stress leading to ERS (Calvaruso et al., 2012). There were significant rise in ROS generation post CBD treatment of MDA-MB-231 cells (Shrivastava et al., 2011). Reports have shown that the GRP78 expression gets upregulated in cells treated exogenously with ceramide (Liu et al., 2014). The ceramide treated cells activate PERK/eIF2α arm of UPR^{ER} that favor ATF4/CHOP upregulation (Liu et al., 2014; Park et al., 2008). Cannabinoid-induced apoptosis shows p-eIF2α mediated p8 activation through ATF4/CHOP (Carracedo et al., 2006). Shrivastava et al., elegantly showed a significant increase in p-eIF2α after CBD treatment of MDA-MB-231 cells (Sanchez et al., 2001). Furthermore, IRE1α/XBP1 pathway of UPR^{ER} also recorded the selection of JNK cascade that favors apoptosis (Liu et al., 2014). ER maintains homeostasis of Ca^{2+} by being the intracellular repertoire of Ca^{2+}. The physiology of elevated Ca^{2+} due to ER stress has been shown in MDA-MB-231 cells after CBD treatment (Ligresti et al., 2006). Exogenous ceramide treatment also causes depletion of ER luminal Ca^{2+} (Liu et al., 2014).

5.2. Expression of p8

The stress-inducible gene, p8 (NUPR1, nuclear protein1), is a multitasking druggable protein with roles in metastasis prevention (Emma et al., 2016; Mallo et al., 1997). Paradoxically it has also been involved in resistance to chemotherapy in breast cancer models (Vincent et al., 2012). Interestingly, the chromosomal mapping locates p8 at 16p11.2, the region that is amplified in breast malignancy (Courjal and Theillet, 1997; Ito et al., 2005). Remarkable studies with p8 siRNA on HeLa and colon carcinoma cell lines congruently elucidated the translational and transcriptional upregulation of ATF4 and CHOP by p8 during ERS (Chen et al., 2015). The same study went on to prove that p8/ATF4/CHOP axis of UPR^{ER} is cardinal in autophagy induction (Chen et al., 2015). In pancreatic model, increased p8 expression was not only in accordance with upregulation of UPR^{ER} target genes; ATF4, CHOP, TRB3 but also with considerable levels of XBP1s mRNA (Carracedo et al., 2006). Studies on cannabinoid treated human glioma cells pronounced the ERS stimulated activation of autophagy through upregulation of p8/TRB3 and inhibition of Akt/mTOR pathway (Salazar et al., 2009). In human breast cancer cell line (HBCCs), challenge with THC led to dose dependent increment in p8 levels (Caffarel et al., 2008).

5.3. Cell cycle arrest and cell survival

One of the extensively studied effects of THC/endocannabinoids with CB1 and CB2 receptors is the control of cell fate via interference in cell cycle progression. THC has been shown to inhibit cell-cycle advancement by G2-M arrest, mediated by CB2 in breast cancer cell lines (Guzman, 2003). In another remarkable study on anti-proliferative action of THC in ER-negative/PR –positive breast cancer cells (EVSA-T cells), transcriptional as well as translational expression levels of JunD were found to be upregulated after THC treatment (Caffarel et al., 2008). JunD, a transcription factor belonging to activator protein-1 (AP-1) family, when overexpressed leads to inhibition of cell proliferation (Weitzman et al., 2000). Thus, THC mediates activation of JunD that reduces tumor proliferation (Caffarel et al., 2008).

Paradoxically in one study on HER2 tumor cell line with CB2 knockout showed that the lack of CB2 not only lessened the number of tumors per animal, but also lowered tumor multiplicity (Perez-Gomez et al., 2015). The study further corroborated that the HER2 showed association with CB2 expression, whereby they displayed the co-localization of HER2 receptor and CB2 protein (forming HER2/CB2 heterodimer). Thus, the study elaborated that CB2 affects the HER2 driven proto-oncogenic signaling. This presented an unprecedented way to combat HER2 action through the therapeutic intervention of CB2 receptors. Also, CB2 can be under potential consideration for being prognostic in HER2 cancer subtype.

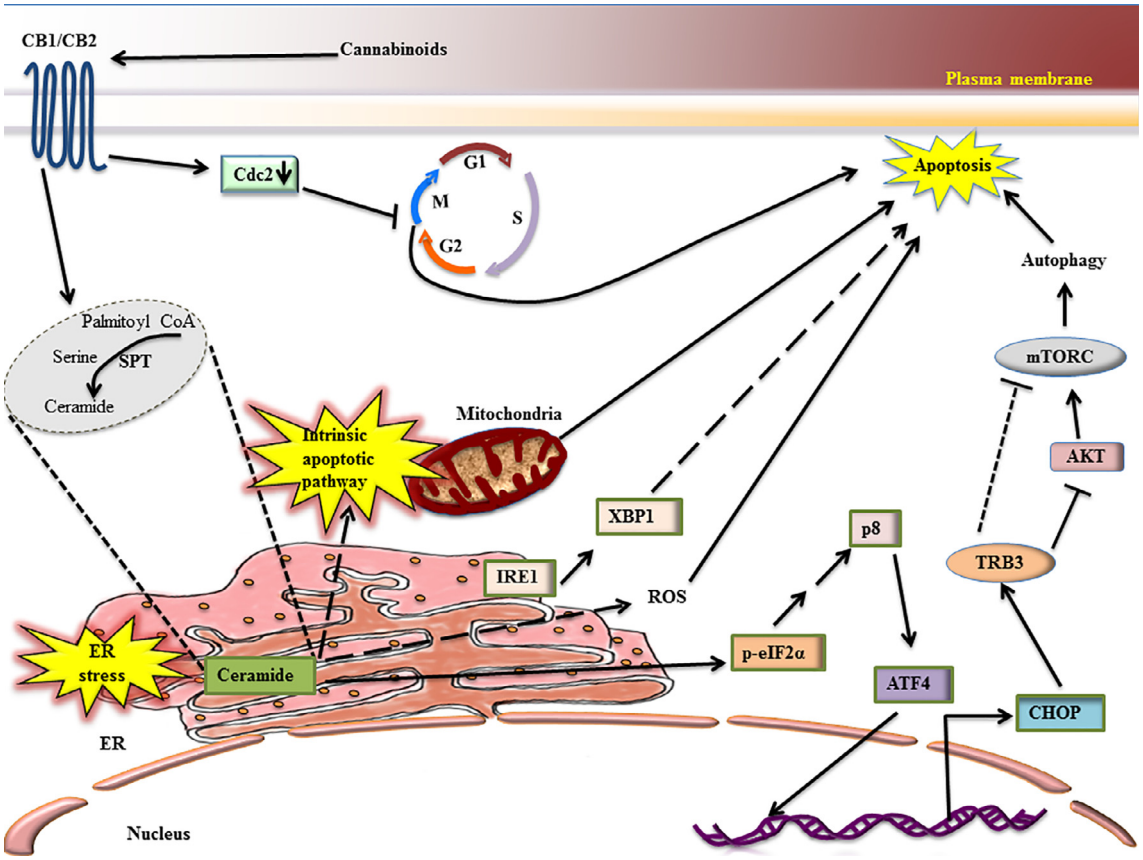

Fig. 3. Mechanism of cannabinoid-induced apoptosis in breast tumor. Treatment of breast tumor with cannabinoids elicits *de novo* synthesis of ceramide in the ER lumen leading to ERS that follows a sequence of events described in the text.

5.4. Autophagy and apoptosis

Autophagy is responsible for protein and organelle turnover thereby acting as housekeeping process in the cell, however irremediable autophagic initiation is known to kill tumors (Calvaruso et al., 2012; Velasco et al., 2016a). During ERS, the molecular mechanism of autophagy commences with the activation of ULK1/2 (unc-51-like kinase 1 and 2) complex, which under normal cellular conditions remains repressed by mTOR (Rashid et al., 2015). The PERK/eIF2α/ATF4 arm of UPR^{ER} potentiates induction of LAMP-3 under hypoxic stress (Mujcic et al., 2009). UPR^{ER} associated activation of PERK/eIF2α arm mediates co-induction of autophagy through TRB3 modification (Cunard, 2013). TRB3 being a negative regulator of Akt, when upregulated, causes deregulation of mTOR thereby aiding in autophagic flux (Cunard, 2013). The animal models of cancer have illustrated autophagy-mediated apoptosis after cannabinoid treatment and this inhibitory effect of THC can be impeded through genetic/pharmacological obstruction of autophagy (Calvaruso et al., 2012). The CB2 mediated anti-tumor action of THC and JWH-133 treated MMTV-neu mice (Her2-positive breast cancer model) has been proved where pro-tumorigenic Akt pathway is inhibited (Caffarel et al., 2010). The same study also proved that THC and JWH-133 challenged MMTV-neu mice showed fading metastases of breast carcinoma in lungs. Shrivastava et al., ascertained lessened intensities of Akt/mTOR pathway with concomitant increase in LC3-II concentrations following CBD treatment in MDA-MB-231 cells, thus validating the autophagic killing of tumorous cells (Shrivastava et al., 2011).

In cannabinoid-induced cell death via ERS, autophagy precedes apoptosis (Fig. 3) (Velasco et al., 2016b). The mitochondrial intrinsic pathway of apoptosis is described as sequelae of consequences: activation of caspase 8, proteolytic cleavage of BID (t-BID), assembly of proapoptotic Bcl2 members (Bax/Bak), mitochondrial membrane permeabilization, leakage of cytochrome c and Smac/DIABLO, caspase 9 and apoptotic protease activating factor1 (APAF1) activation (Galluzzi et al., 2014; Wang et al., 2017). Shrivastava et al., showed caspase 8 mediated activation of t-BID in CBD treated MDA-MB-231 cells, which lead to cytochrome c and Smac leakage into the cytosol, thus authenticating mitochondria-mediated apoptosis. They further implicated the role of mitochondria-mediated apoptosis through inhibition of caspase, which diminished the levels of apoptotic proteins in breast cancer cells (Shrivastava et al., 2011).

The ERS induced activation of IRE1/XBP1 axis leads to the apoptotic pathway. The p-eIF2α/p8/ATF4/CHOP axis activates TRB3, which deregulates Akt/mTOR pathway causing autophagy induction (Calvaruso et al., 2012; Carracedo et al., 2006; Maccarrone et al., 2014; Salazar et al., 2009). The rise in ceramide concentration causes ROS accumulation thereby favoring apoptosis. Also, the rising ceramide concentration elicits the intrinsic apoptotic pathway in mitochondria culminating in apoptosis (Calvaruso et al., 2012). The effect of cannabinoid treatment also disseminates to blockage of G2-M transition in cell cycle through lowering the levels of Cdc2 [cyclin-dependent kinase 1 (Cdk1)] thereby stimulating apoptosis that decreases tumor proliferation (Caffarel et al., 2006) (Fig. 3).

6. Clinical use of Cannabinoids: Palliation

Apart from the above discussion about the role of UPR^{ER} induction after cannabinoid treatment in either cell lines or animal/

xenograft models, it is plausible here to mention about the current use of cannabinoids in palliation. THC has been attributed to promote appetite in CB1 mediated pathway (Sofia et al., 1973). One Phase III clinical trial supported palliative use of THC in evoking appetite and inhibition of wasting (Velasco et al., 2012). Anandamide, THC and some synthetic cannabinoids have been proven to be effective in acute pain (Fride and Mechoulam, 1993; Sofia et al., 1973). Endocannabinoids have been reported to show antinociceptive effect on central nervous system and spinal cord (Pacher et al., 2006). Ancient documents have reported the use of cannabinoids in the treatment of pain (Mechoulam, 1986; Pertwee, 2009a). Documents support the effectiveness of anandamide against chronic pain due to inflammation and neuropathy (Guindon and Beaulieu, 2006; Guindon et al., 2006). THC has been used as antiemetic and analgesic in chemotherapy receiving patients (Carey et al., 1983; Noyes et al., 1975). The antiemetic effect of cannabinoid is well known in chemotherapy-induced nausea and vomiting (Guzman, 2003; Pertwee, 2009b).

7. Conclusion

The number of lives claimed by breast cancer owes to the invasion of cancerous cells to nearby healthy tissues. A single stratagem of chemotherapy doesn't reduce the rate of mortality, hence the time demands for targeted rational therapies that effectively destroy molecules supporting cancer. Therefore the antiproliferative role of cannabinoids, well proven with the underlying mechanistic details, makes them a suitable therapeutic chemical. Albeit the psychoactive THC has been studied in marijuana consumers to impose toxicity by inducing cell death and DNA fragmentation of neurons, the use of THC in palliative and antineoplastic activity can't be overlooked.

Various researches have presented accumulating data on the efficacy of cannabinoid treatment on breast cancer cell lines. THC and CBD especially, have been effective against HER2 and TNBC breast cancer cell lines (Caffarel et al., 2010; Murase et al., 2014). In conventional therapy of HER2 tumors, Trastuzumab (Herceptin, a humanized neutralizing monoclonal antibody against HER2) usage gave 75% of non-responding patients while 15% of the responders ultimately showed metastasis (Hynes and Lane, 2005). The research conducted on genetically modified MMTV-neu mouse model illustrated the mitigating effects of THC and JWH-133 on tumor progression (Caffarel et al., 2010).

Some pilot clinical studies are already underway where patients with glioma are challenged with THC (Guzman et al., 2006). However, the time needs extensive and elucidative investigations on the involvement of UPR^{ER} in breast cancer, both *in vitro* as well as *in vivo*. The antineoplastic properties of cannabinoids, which exploits UPR^{ER} and its signaling alliances, have been well shown in cell lines and xenografts. The involvement of various UPR^{ER} markers like upregulation of GRP78 and the subsequent activation of PERK and IRE1 signaling have been well studied in various breast cancer cell lines but data is lacking for the participation status of ATF6 in cannabinoid treated tumor models. We need to emphasize on more such studies that can prove the cannabinoid-mediated UPR^{ER} upregulation for checking proliferation of breast malignancies. Many such studies as discussed in the present review do support the efficacy of cannabinoids as drug that maneuvers UPR^{ER} to halt tumor progression, but lack of conclusive clinical trials in breast malignancy raises concerns on using cannabinoids as drug against breast cancer. In summary, the quintessential role of cannabinoid in killing tumor has been widely studied, but future research is the requirement for solving the problem related to cannabinoid treatment in breast cancer.

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