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# How to Attain Clinical Translation Using Interactions Amongst Endoplasmic Reticulum Stress and Ferroptosis as Therapeutic targets for Improvement of Outcomes & Prognosis of Ovarian Cancers: A Comprehensive Narrative Review

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**Abstract:**

Ferroptosis portrays a distinct kind of cell demise, guided by iron based phospholipid peroxidation, as well as mechanistic modes basically implicated in iron metabolism, dysequilibrium of the antioxidant system in addition to accrual of lipid peroxides.Protein processing alongwith folding in the endoplasmic reticulum(ER) are intricately associated with controlling events which estimate cellworking ,fate as well as their survival .The nonregulatedproliferation capacity of malignant cellsforms an unattractive microenvironment which have properties ofgreater metabolic needs, nutrient deprivationas well as metabolic acidosis , facilitates the accrual of misfolded in addition to unfolded proteins in thelumen ofER causing activation of the unfolded protein responses(UPR) that resultsin endoplasmic reticulum stress(ERS). Ferroptosis& ERS share pathways in variable diseases in addition to the two crosstalk for influencing cell fate, survival and demise. Moreover, cell demise pathways are not simply linear signaling stepwise patterns as well as variable cell demise pathways might be correlated at plethora of levels. Ferroptosis& ERS in ovarian cancer (OC)have evoked considerable attention of scientific researchers, nevertheless, the two have not been detailed in togetherness with regards to OC, as well as their crosstalk studies are not present. In this narrative review we describe the plausible association amongst Ferroptosis& ERS to yield grounds for generating therapeutic strategies for managing OC.

**Keywords:** Ferroptosis; endoplasmic reticulum stress (ERS); ovarian cancer (OC); unfolded protein responses (UPR)

## Introduction:

Ovarian Cancer(OC) portrays the third most frequently encounteredgynaecolgical malignancies, of the female reproductive system,whosediagnosis had been made as well as possesses greater mortality rates offull gynaecolgical tumor spectrum [1]. In view of itspernicious characteristics at the time of earlier stages, maximum of patients with OC get diagnosis made at substantially advancement stage of the OC to start with at the time when primary debulking surgery, adjuvant chemotherapy, radiotherapy, immunotherapies are not devoid of their inimical sequelae which has been a well displayed fact inclusive of recurrencerates, metastasis, resistanceto chemotherapy, thereby OCisassociated with substantially greater mortality rates[2]. In view of the escalating incidence in each year with escalating young persons generating OC [3,], the requirement of generating innovative methodologies in addition tobiomarkers which might aid in earlier determination along with greaterefficacious therapies subsequent to diagnosis is assuming considerable significance [4].

Ferroptosis portrays a kind of cell demise, unique from other kinds of programmed cell death for instan ceapoptosis, autophagy in addition to necroptosis where ROS along with lipid peroxides (LPO) accrual get generated by iron metabolism as well as their for generating fatal toxicity in view of cells are not capable of metabolizing the min a smooth manner[5]. Whereas canonicaltreatments generally deplete tumor cells by stimulating cell death for generation of resistanceit has assumed considerable significance for scientific researchers for cancer treatment, acknowledged its part in controlling cell demise [6]. Variable studies have illustrated that ferroptosis is correlated with resistance to cancer therapies, which might beplausibly involved in aiding in reverting resistance to cancer therapies [7]. Once further advancements of scientific research occurred invention of ferroptosis proved tobecrucial in plethora of variety of diseases inclusive of Breast cancer (BC),pancreaticcancer, neurological diseases, cardiovascular disease(CVD) alongwith kidney diseases,and others[8].Of these,ferroptosis is maximum intricately correlated with malignant tumors in addition totumor cells possesspronounced sensitivity to ferroptosis[9]. Ferroptosis possesses the capability of controlling the generation of OC via variable mechanistic modesor etiological factors, therefore escalates the sensitivity of OC cells towards ferroptosis targeted therapeutics, as well as taking care of chemotherapy resistance [10], therefore escalating the effectiveness of chemotherapeutic agents for the treatment of OC [11]. Furthermore, a correlated study has displayed that the fashion of immune infiltration in addition to correlated genetic characteristic of ferroptosis, plausibly might be used for anticipation of prognosis of OC cases [12]. Utilization of combination of ferroptosis with





chemotherapy, nanotechnology, X-raytherapy along with photo dynamic therapy have been displayed to result in improvement of therapeutic effectiveness[13], that yield plausible targets as well as generating innovative therapeutic trajectories for ferroptosis in reference to OC management.

The endoplasmic reticulum (ER) stressis implicated in lipidmetabolism, controlling of $Ca^{2+}$ , in addition toprocessing of protein, their folding along withtransportation, thatportrays a significant organelle in case of eukaryotic cells[14]. ERstress (ERS)gets stimulated in cells by hypoxic situations,ii)geneticmutations,iii) insufficiency of nutrients as well as iv)oxidative stress( OS), that resultsin accrual ofmisfolded in addition to unfolded proteins in thelumen ofER causing activation of the unfolded protein responses(UPR) for taking care of the external milieu, which isunattractive[15]. Nevertheless, sustenance of greater magnitude of ERS leads to cell demise, once threshold for tolerance of ERS gets crossed[16], possesses the capability of resultingin generation of variable diseases forinstance cancer, atherosclerosis, diabetic retinopathy, in addition toischaemic nephropathy[17]. The inimical tumor microenvironment( TME) for tumor cells in view of greater metabolic needalong withOS,of rest disrupts ERhomeostasis in the immune cells that has the capability of influencing protection conferring anticancer immunity[18]. Yan et al. [19], illustrated that targeting the germane pathways in ERS are capable of hampering the proliferation of OC cells along with decrease chemotherapy resistance[19]. Thereby ERS is crucial in the formation as well as forOS therapy.

Different studies have illustrated that ferroptosis in addition to ERS possess theakin controlling pathways, along with the two possess the capacity of changing the generation of variable diseases by crosstalking witheach other[20-22].

Earlierwe reviewed the cell death mechanisms as plausible therapeutictargets for BC, role of melatonin as a future prospective therapyfor treating nonalcoholic fatty liver disease(NAFLD) bytargeting hepatic ferroptosis ,and its part in treating diabetic kidney disease(DKD) [23-25]. Here we further update themechanistic modes of ferroptosis along with ERSin OS as well asthe plausiblegermaneness of the twoof them for emphasizing the generation of innovative approaches in addition to plausibletargetsforOC therapy .

**Methods**

Here we conducted a narrative review utilizing search engine pubmed,google scholar ;web of science ;embase;Cochrane reviewlibraryutilizingthe MeSH termslike endoplasmic reticulum stress(ERS); ovarian cancer(OC); unfolded protein responses(UPR); ferroptosis; glutathioneperoxidase 4 (GPX4); lipid peroxidation; Divalent metal transporter(DMT); Ferritin ; Oxidative stress( OS); Ferritinophagy ; AMPK; nuclear factor erythroid-2-related factor-2((Nrf2**)** /Kelch-like-epichlorohydrin (ECH)-associated protein 1 (KEAP1); Herbal products; curcumin analogs ; melatonin from2000 to 2025 till date.

**Results**

We found a total of 2000 articles out of which we selected190 articles for this review.No meta-analysis was done.

## 2. Ferroptosis in case of OC

Ferroptosis portrays a kind of programmed cell death that possesses the properties of escalated accrual of iron, lipidantioxidation along with lipid peroxidation [26]. OC casesgenerally display chemotherapy resistance which is intricately associated with ferroptosis[27].

### 2.1 Iron metabolism in case of OC

**Iron** portrays one of the imperative trace elements that possess significant part in human growth as well asgeneration, energy metabolism in addition to working of the immune system[28]. Aberrations of the iron metabolism influenceredox reactions,ii) genecontrolling,iii) enzymatic reactions iv) DNA generation in addition to healing[29]. Iron possesses complicated nature along with comprehensive circulating mechanistic modes for guaranteeing its appropriate organization, utility as well asstorage for sustenance of precise in addition to nontoxic cellular iron quantities in human body [30]. Existence of iron in human body is in the form of 2 kinds off erric iron ($Fe^{3+}$) along with $Fe^{2+}$, as well as there is presence of variable transporters/ modes based on variable iron kinds. Dietary iron ingestion/day is inclusive of haem iron in addition tononhaem iron[31]. Once they reach theintestinal lumen in the form of $Fe^{3+}$ their reduction takes place to $Fe^{2+}$,by duodenal cytochrome- B fortheir absorption,where nonhaem iron absorption takes place in the intestine through divalent metal transporter(DMT)1 protein [32] . Transportation of heme iron subsequently takes place to duodenal epithelium through haem protein 1 followed by itsabsorption, internalization, degradation into $Fe^{2+}$, in addition to hemeoxygenase-1(HO1) [33]. Following that iron might continue to stay in theenterocytes or gain entry into the blood stream from basolateral membrane of the intestinal epithelial cells through membrane iron transporter protein 1, whereas undergoingoxidation byferrousoxidaseorceruloplasmin for forming $Fe^{3+}$ [34]. On gaining entry into the blood stream, plasma transferrin(TF) guarantees precise organization of $Fe^{3+}$ right through the cells of human body for utilizationby variable organs for forming iron possessing constituents via TF receptor(TFR) modulatedholoTF endocytoses [35].For instance, hepaticgeneration of hemosiderin takes place, whereas myoglobin gets generated in the muscle tissue, with the Bone marrow contributing to thedevelopment of the redblood cells(RBC) possessinghaemoglobin. Iron uptake gets facilitated in cells basically via the TF along with TFR systems, as well as $Fe^{3+}$ gets reduced to $Fe^{2+}$,by ferric oxidereductase, whosebinding takes place to ferritin, to generate storage iron, with the little percentage gaining entry into thecytoplasm which overallcontributes to the labile ironpool(LIP) [36]. In view of instability in addition to greater susceptibility to oxidation of $Fe^{2+}$, escalated iron ions causethe generation of reactive oxygen species(ROS) , thatfacilitates lipid peroxidation via the Fenton reaction[37], therefore resultingin oxidative injury to the lipid membranes, proteins along with DNA eventually resultingin cell demise[38]. Out of the 3 mechanistic modes of ferroptosis,escalated accrual of $Fe^{2+}$, in the LIP iron escalates the sensitivity of cells to ferroptosis as well as portray the starting constituents implicated inferroptosis generation[36].

The starting step of ferroptosis has notbeen isolated till now, however ferroptosis has been intricately associated with the intracellular quantities of free iron[39].Iron metabolismworksin the form ofa crucial pathophysiology of OC, in addition to the magnitude of intracellular iron accrual functions as possessing amajor part in the time period of OC[40]. Concomitantly aberrations in the iron metabolism, particularly the attaining of iron accrual along with sustenance of enhancediron aid in theevent of tumorigenesis as well astumorgrowth[41]. Iron accrualescalatesthe risk ofgenerationofdiseases forinstance cancer in addition to injury to tissues[42]. Thereby sustenance of intracellulariron ions homeostasis is crucial.As per Basuli etal. [43], OC starting cells, display greater iron reliance. Escalated iron export further diminished the proliferation along with invasion of OC starting cells as well as on the other hand,escalated iron uptake escalatesOC proliferation along with invasion[43]. Starting of high grade serous ovarian cancers(HGSOC) canonically occursfrom thefallopian tubes with diagnosis usually postponed till FIGOstageIII-IV in view of its asymptomatic presentation,in addition to iron quantities of HGSOC have been found to be correlated with greater in contrast to low grade serous Ovarian Cancer (LGSOC), pointing that HGSOC along with iron metabolism are robustly correlated [44]. Additionally, the malignant conversion as





well asmetastasis of cancer cells are intricately correlated with alterations of cellularredox status[45]. The molecular injury resulting from escalated quantities of inimical reactive oxygen species(ROS) ROS which gets catalyzed by free iron is usually knownas ''oxidative injury'' as well as Bauckman etal. [46], displayed that ROS possesses the capability of conversion normal ovarian by facilitating the mitogen activated protein kinase(MAPK) pathway. Apart fromthat ROS possess the capacity of hydroxylating DNA residues for the formation of substantially mutagenic 8 hydroxy-2' deoxy guanosine(8OHdG),whose quantities have been observed to be correlated with badprognosis in case of HGSOC patients[47]. Binding of iron polyporphyrinheme occurswith p53, that resultsin disturbance of p53-DNA crosstalk, that results in nuclear export as well as cellularbreakdown of p53 in addition toescalated proneness to HGSOC[48]. Basuli etal. [43],reported that escalated iron concurrently influenced tumor cell proliferation, metabolism along with metastasis. Enhancing the expression of ferroportin on cell membranes [49], diminishing iron consumption[50],or diminishing the quantities of TF[51], along with TFR *in vivo* [52], possesses the capability of hampering tumor growth . Apart fromthat iron metabolism has the capacity of generating OC by controlling Hypoxia inducible factor1α(HIF 1α). HIF 1αstimulates the propagation of OC byhampering the working of p53, facilitating Interleukin (IL-6) expression, or getting controlled by Longnon coding RNAs(lnc RNAs) [53]. Iron metabolism further is intricately associated with chemotherapy resistance as well as solutecarrier familygeneration40members 1 (SLC40A1), that is an iron metabolism associatedgene, portrayingthelone acknowledgedgene that exports iron[54],thatpossesses a critical part in the transportation of iron from the intracellular milieu to the extracellular milieu, thereby physiological expression of SLC40A1 possesses a critical part in the controlling of iron homeostasis. SLC40A1 stimulated iron overload resultsin cisplatin chemotherapy resistance in OC[55]. SLC40A1 upregulation diminishes cisplatin resistance by iron export, diminishing intracellular iron quantities in addition to OS. In contrast to that escalated iron quantities along with OS resulting fromSLC40A1 downregulationescalates cisplatin resistance[55]. Thereby modulation of iron quantities for affecting redox systems might be a plausible approach for reverting chemotherapy resistance in OC.

Theiron based quality of OC tumor starting cells further escalates their sensitivity to ferroptosis in addition to ironchelators, which yieldthemas plausible therapeutic targets for OC therapy [56].A natural ironchelatordesferrioxamine[72], has beenutilized for iron overload, has demonstrated favourableoutcomesfor OC therapy.Wang etal. [57],investigated the actions of desferrioxamine on OC cancer cell lines as well as their observations were that desferrioxamine apart from hamperingcancerstem cells, they further escalated effectiveness of cisplatin chemotherapy, resultedin improvementof chemotherapy resistance along withcontinuation of time ofsurvival. Furthermore, there is proof of other agents whichcontrol iron metabolism as well as might possess actions on other biological events. Forinstance the antimalarialdrug artemisinin, has been recognized forits antimalarial, anti inflammatory in addition to anti tumor actions in addition to its compounds(forinstance artemisunate) possesses the capability of diminishing cell proliferation as well as stimulate ROS generation in the OC cells[58]. Artemisunate has the capability of activatinglysosomal working ,resultingin facilitating breakdown of ferritin, resultingin liberation of iron in lysosomes, therefore modulatingcell demise[59]. Controllers, inclusive of iron uptake associatedcontrollers[60], iron storage associatedcontrollers[61], along with iron transportation associatedcontrollers[62], impact the events of OC via the controlling of iron metabolism quantities.

**2.2 Lipid peroxidation in case of OC**

Ferroptosis portrays a kind ofcell demise, unique from other kinds of programmed cell death forinstanceapoptosis, autophagy in addition to necroptosis resulting from membrane lipid peroxidation along with considerable accrual of ROS[63]. Additionally,membrane lipids possess a significant part in the controlling of the fateof cell as well as lipid metabolism thatiselemental in estimating the fateofferroptosis[64], in addition to is crucial forimplementation offerroptosis.

Out of the different lipids , polyunsaturated fatty acids(PUFA), along with variable phospholipids(PL's) forinstance phosphatidylethanolamine (PE ), as well asphosphatidyl cholineare implicated in lipid peroxidation in case of ferroptosis .PL's thatpossess PUFA's have greater proneness for oxidation, however lesser oxidizable saturated fatty acids /monounsaturated fatty acids conferred protection to the cell from ferroptosis[65]. Thereby the enzymes along with pathways implicated in controlling PUFA's in addition to monounsaturated fatty acids metabolism, apart from equilibrium of PUFA's in addition to monounsaturated fatty acids in membrane PL's, are capable of affectingcellular sensitivity to ferroptosis[66]. The observations of the above-mentionedfact yieldsinnovative approach for the therapy of lipid peroxidation in case of OC ferroptosis. In view of membrane PL's of PUFA's which guideROS generation catalyzed by iron ions, crosstalk with PUFA's are implicated in stimulating lipid peroxidation that resultsincellular ferroptosis, as well asnotjustby free PUFA's by themselves, the enzymes which are involved in the binding of the free PUFA's to PL's, possess a critical partin ferroptosis[66]. Acyl-CoA synthetase long-chain family member 4 (ACSL4) portrays animperative constituent of ferroptosis achievement, the manner displayed by microarray evaluationof cell lines with resistanceto ferroptosis along with utilization of genome wide clustered regularly Interspersed shortpalindromic repeats nuclease(s) (CRISPR) dependent screening system[67]. ACSL4 catalyzes free long chain fatty acids(LCFAs) to Acyl-CoA by associating them with CoA.Inserting Acyl-CoA into membrane PL's followed by binding to the PE to generate PUFA's PL's ,gets catalyzed by the enzymelysophosphatidylcholine acyltransferase 3 (LPC AT3) [68].In reference to mechanistic modes,2 basically modesareimplicated i) non enzymatic spontaneousoxidation as well asii) enzymes modulated lipid peroxidation[69], leading to the formation of phospholipid-peroxide (PL-OOH) in addition to once converting of PL-OOH does not takes place to phospholipidhydroxide (PL-OH ) by antioxidantsin the required time it leadsto considerable accrual of PL-OOH, which resultsin considerable lipid peroxidation along with activation of the antioxidant system, stimulating injury to the cell membrane, eventually resultingincell impairment as well as ferroptosis[70]. Non enzymatic lipid peroxidation alias lipid autooxidation represents free radicals guided chain reactions . Reaction of hydrogenperoxide($H_2O_2$)with $Fe^{2+}$, resultsin theformation ofhydroxyl radical $(OH)^{-\bullet}$ , whose reaction takes place with PUFA's in the plasma membrane(PM) in the Fenton reaction for generating lipidperoxides (LPO) resulting in ferroptosis[71,72]. Therebyescalated accrual of LPO is imperative for escalating the effectiveness of ferroptosis [73], in addition to $OH^{-\bullet}$ portray themaximumactive ROS [74], therebyit works in the form of an innovative therapeutic target forthe OC treatment through chemodynamic therapy(CDT). $H_2O_2$ nano-enzymes generated in cells by Sun etal. [75], by utilization of CoNi alloysencapsulated nitrogen doped carbonnanotubes displayed glucose oxidase as well as lactate oxidaseactions for efficaciously interfering with the antioxidant defense system by catalyzing the $OH^{-\bullet}$generation, escalating the ROS quantities in the tumor microenvironment( TME) in addition toinjuring tumor cells, whereas eliminatingglutathione(GSH) for stimulating ferroptosis in the tumor cells[90]. Liang etal. [76], illustratedpoly dopamine(PDA)- modulated Michael additionin combination with $Fe^{2+}$ elimination of GSH, escalated accrual of $OH^{-\bullet}$, eventually led to escalated intracellular liberation of chemotherapeuticagent Doxorubicin (DOX), thereby stimulating ferroptosis [76]. Additionally,lipid peroxidationis robustlyassociated with variable metabolic along with signaling pathways forinstance cytochrome P450 oxidoreductase(POR) pathway as well as enzymes which possessiron inclusive of lipooxygenases(LOX) further aids in lipid peroxidation[77]. On the other hand, enzymatic lipid peroxidation representsan event that directly implicates oxidation of free PUFA's in**to** different kinds of lipidhydroperoxides catalyzed by LOX[78]. Out of these, the arachidonate familylipooxygenase(ALOX) control lipid peroxidation. Binding of5 LOX to the microsomal GSH-S transferase 1resultedin diminishedlipid peroxidation in addition to modulated ferroptosis in the cancer cells[79]. On the other hand, Chu etal. [80], found that ALOX12 (alias LOX12) manipulated lipid peroxidation was involved in p53 based ferroptotic reactions in case ofROS stimulated stress [80], whereas the expression quantities of arachidonate family 15 lipooxygenase (ALOX15), are correlated with



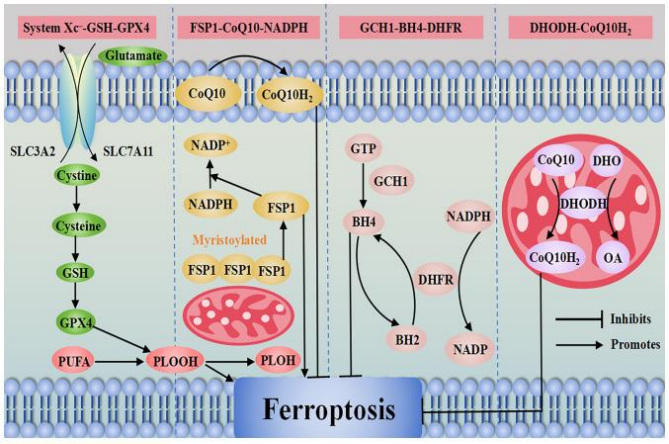



spermidine/spermine acetyltransferase (SAT1) gene, a transcriptional target of p53[81]. Zhang etal. [82], illustrated that the chemotherapeutic agents for OC stimulated escalated lipid peroxidation via ROS starting ovarian cells ferroptosis, thereby resulting in ovarian cell demise [82].Asper Xuetal. [83], p53 works in the form of a significant factor in the ferroptosis event [83]. p53 displays bidirectional controlling actions dependent on particular situations of encompassing milieu. In case of lesser quantities of lipid peroxidation p53 hampers the event of ferroptosis, facilitating cell survival. Nevertheless, on continuation of escalated lipid peroxidation, ferroptosis is stimulated [83].

Taken together, future studies on the actions of variable lipid metabolic pathways regarding lipid peroxidation along with regarding ferroptosis from the point of view of chemotherapy stimulated OS as well asferroptosis might aid in regulating ovarian injury, causing improvementof quality of life (QOL) of OC patients might aid in gettinginsight regarding ferroptosis in addition to therapeutic OC.

**2.3 Lipid antioxidation in case of OC**

Oxidative injury takes place in view of disequilibrium amongst cellularantioxidant system with thegeneration of the free radicals in addition to neutralization or depletion of their inimical actions. ROS modulated lipid peroxidation, portrays a critical step in guidingcellular ferroptosis along withinactivation of antioxidant system portrays the basic etiological factor of ferroptosis[84]. Currently it has been illustrated that the basic antioxidant system controlling ferroptosis is inclusive of i) *System Xc* (*-*) -glutathione (GSH) -glutathione peroxidase4(GPX4) pathwayii) ferroptosis suppressor protein 1 (FSP1)/ - coenzyme Q10 (CoQ10) pathwayiiI) GTPcyclohydrolase1(GCH1)- Tetrahydrobiopterin (BH4) pathway IV)dihydroorotate dehydrogenase(DHODH) -CoQH2 pathway. Out of these,*System Xc* (*-*) -glutathione(GSH) -glutathioneperoxidase4(GPX4) pathway portrays the maximum elemental antioxidant system that possesses the crucial part in conferringprotection ferroptosis[85].Figure 1yields asummaryof basic antioxidant system controlling ferroptosis[rev in ref 86].




Legend forFigure1

Courtesy reference no-86Primary antioxidant systems regulating ferroptosis. System Xc⁻-GSH-GPX4: Cystine is oxidized to cysteine through the System Xc-, which leads to the synthesis of GSH, and GPX4 reduces PLOOH to PLOH with the participation of GSH, which induces the onset of ferroptosis when GPX4 is inhibited. FSP1-CoQ10-NADPH: FSP1 promotes the transfer of CoQ10 from mitochondria to the cell membrane by myristoylation of the N-terminus with the participation of CoQ10 and its reduction to $CoQ10H_2$ catalyzed by NADPH, which prevents cellular ferroptosis by trapping free radicals. GCH1-BH4-DHFR: GCH1 is the rate-limiting enzyme for the biosynthesis of BH4. BH4 acts as a free radical-trapping antioxidant, inhibiting ferroptosis. It is recycled by DHFR and subjected to redox cycling. DHODH-$CoQ10H_2$: DHODH is located on the outer surface of the inner mitochondrial membrane and inhibits cellular ferroptosis by reducing lipid reactive oxygen species in mitochondria by reducing CoQ10 to $CoQ10H_2$. Supplementation with DHODH substrates or products (DHO or OA) regulates cellular ferroptosis. BH2, dihydrobiopterin; BH4, tetrahydrobiopterin; CoQ10, CoQ10, coenzyme Q10; $CoQ10H_2$, ubiquinol-10; DHFR, dihydrofolate reductase; DHO, dihydroorotate; DHODH, dihydroorotate dehydrogenase; FSP1, ferroptosis suppressor protein 1; GCH1, guanosine triphosphate cyclohydrolase 1; GSH, glutathione; GPX4, glutathione peroxidase 4; OA, orotate; PLOH, phospholipid hydroxide; PLOOH, phospholipid hydroperoxide; PUFA, polyunsaturated fatty acid; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11.

**2.3.A- *System Xc* (*-*) -glutathione (GSH) -glutathioneperoxidase4(GPX4) pathway-**

This possesses the crucial part regarding antioxidant defence mechanistic modes of ferroptosis. *System Xc* (*-*)portrays a cystine-glutamate reverse transporterreceptor) protein that is constituted ofa dimer of solutecarrier familygeneration7member 11 (SLC7A11), along with SLC3A2 that has placement on the cell membrane[85]. *System Xc* (*-*) oxidizes intracellular cystine to cysteine that further causes transformation to GSH [87]. In contrastGPX4, confers protection to the cells against ferroptosis by diminishing PL-OOH transformation to PL-OH which has no toxicity, that implicatesGSH(the reducingcofactor for GPX4) [88]. Hampering of GPX4 stimulateslipid ROS as well as stimulated starting offerroptosis, therefore hampering tumor cells proliferation[90].

Studies have illustrated that erastin[27], sorafenib[91],sulfasalanazine[92], in addition to p53[93], hadthe capacity of generating GSH stimulateferroptosis by hampering *System Xc.* Metallothionen-1Gportrays a crucial factor as well as plausible therapeutictarget for controlling sorafenib resistance in human hepatocellular carcinoma(HCC) . Downregulation of metallothionen-1G escalated lipid peroxidation along with GSH elimination ,resultingin ferroptosis in HCC[91]. Utilization of an innovative strategy was done by Yuan etal. [94], byusing a combination of chemotherapy as well as chemodynamic-therapy, that hampered malignant cells proliferation by inactivation of GPX4 by stimulating GSH elimination, in addition to astrategy that illustrated extensive magnitude of biosafety. Luo etal. [95], observed that paired box8( PAX8- that portrays a GPX4 based OC prone gene) elimination, resulted in escalated sensitivity to GPX4 hampering agents. A combination of PAX8 hampering agents in addition to RSL3, hampered proliferation along with stimulated ferroptosis inOC cells[95]. Apart fromt hat, *System Xc* (*-*) - GSH) - (GPX4) pathway portrays a crucial antioxidant system, causing avoidance of lipid peroxidation modulated ferroptosis as well as blockade of such pathway facilitate the initiation of ferroptosis in stimulating chemotherapeutic resistance[96]. Okuno etal. [97], displayed that *System Xc* (*-*)portrays a transporter that is implicated in cystine in addition to glutamate transport possesses a controlling part in intracellular GSH quantities along with cisplatin resistance in OCcelllines[97].Their outcomes illustrated that OC cells in the cisplatinresistant variant possessed a4.5 time greater cystine uptake as well as intracellular GSH quantities in contrast to OCcelllines in view of their attaining cystine transporteraction that gotmodulated by *System Xc* (*-*):nevertheless, the GSH quantities diminishedsubsequent to glutamate over dosage . Cystine uptake was further hampered. Thereby it gets pointed that *System Xc* (*-*)possesses a significant partin the sustenance of greater GSH quantities in addition to hasthe capacity of conferring cisplatin resistance in OC celllines. Apart fromthat, a study has illustrated that liberation of GSH along with cysteine in case ofOC fibroblasts aid in the diminishing of nuclear accrual of platinum[97]. Furthermore, $CD8^+$T cells are capable of hampering resistance by controlling GSH as well as cysteine metabolism in fibroblasts[98].

Collectively, these suggest that hampering of *System Xc,* elimination of GSH in addition to diminishing of GPX4, together modulate metabolic events that are implicated in amino acids which escalate sensitivity to ferroptosis hampering agents, as well as targeting such systems might have the capacity of reverting chemotherapeutic resistance in addition to diminish the OC propagation.

**2.3.B Ferroptosis suppressor protein 1 (FSP1)/ - coenzyme Q10 (CoQ10) pathway**

Bersuker etal. [99], isolated FSP in the form of arobust resistance factorto ferroptosis, indicating that FSP- CoQ10- nicotinamide adenine nucleotide phosphate(NADPH )pathway is independent of the canonical *System Xc*- GSH- GPX4 pathway, emphasizingone extra pathway implicated inantioxidant controlling of ferroptosis, pointing that its pharmacological hampering might escalate sensitivity of cancer cells to ferroptosis stimulating chemotherapeutic agents. FSP1 portrays a crucial protein which results in avoidance of cells going through ferroptosis, along with FSP1 knock out (KO) escalate sensitivity cell lines to ferroptosis stimulating agents in addition to in






the form of a controller of mitochondrial apoptosis. Enrollment of FSP1 takes place toPM, through myristoylation (a fatty acid modification acknowledged to work in membrane targeting), therefore hampering ferroptosis[99,100]. Basically FSP1 iscorrelated with outer mitochondrial membrane(OMM) as well asgoesthrough myristoylation, at the N terminalend for facilitating transportation of CoQ10 from mitochondria to the cell membrane. The reduction of CoQ10 to the Ubiquinol ($CoQ_{10}H_2$) leads to trapping of the free radicals, modulating lipid peroxidation, in addition to thereby avoidance of ferroptosis of cells[99]. Additionally,ithas been illustrated that subsequenttoStearoylCoA desaturase 1 downregulation, diminishing of lipophilic antioxidant CoQ10, that stimulatesthe plausibility for ferroptosis by hampering intracellular formation of lipids that confersprotection . Hampering of StearoylCoA desaturase 1 escalated the antitumor actions of ferroptosis stimulators in case of OCcelllines. Combination of StearoylCoA desaturase 1 hampering agents with the ferroptosis stimulators might yieldan innovative approach for the treatment of OC[101]. The small molecule hampering agent FIN56 hampers CoQ10formation in the mevalonate pathwaysubsequenttobinding followed by activation of squalene synthase leadingto diminished CoQ10 quantities, therefore escalating ferroptosis sensitivity [102].

Yang etal. [103], generated nanogels that escalated cellularlipid peroxidation via hampering FSP- CoQ10- NADPH pathway, resultingin ferroptosis of immunogeniccells along with leadingto efficacious tumor attrition as well as immune reactions in mouse model of breast cancer. Furthermore, FSP1 downregulation inHCC facilitated sorafenib stimulated ferroptosis [104].

Thereby, FSP- CoQ10- NADPH )pathway, might becomplementary as well as act with the *System Xc* GSH- GPX4 pathway for hampering lipid peroxidation in ferroptosis, yielding plausible therapeutic approach for the treatment of OC .

**2.3.C. GCH1)- BH4- dihydrofolate reductase (DHFR) pathway-**

An earlier study isolated the GCH1- BH4- DHFR pathway in the form of alternative complementary mechanistic mode for *System Xc* - GSH- GPX4 pathway [105]. GCH1 portrays a rate restricting enzyme regarding BH4 generation, that facilitates ferroptosis through the metabolites BH4 in addition to dihydrobiopterin (BH2). BH4 in the form of free radicals trapping antioxidant, is capable of getting recycled by DHFR for redoxcycling, along with BH4 possesses the capability of antioxidant breaking down actionson phospholipids(PL's), thatpossesstwo PUFA tails as well asavoidance of lipid peroxidation in addition to thereby ferroptosis by hampering the generation of LPO's[105].

Viadirect trapping of antioxidant free radicals along with generation of CoQ10[105], once GCH1 upregulation takes place,it facilitates BH4 generationas well asmitigates the inimical actionsof RSL3 stimulated cellular ferroptosis. Furthermore, GCH1 overexpression has been illustrated to diminish the sensitivity of cancer cells that have chemotherapy resistance to ferroptosis, that inturn further attenuated propagation of ferroptosis of cancer cells via controlling of CoQ10 [106].

Apart from that, germane studies have illustrated involvementof BH4 in dopamine generation, nitric oxide synthase (NOS), as well as melatonin[107], while exogenous dopamine or melatonin , hadthe capacity ofhampering ferroptosis[108]. Variable studies have illustrated that nitric oxide (NO), possesses the capability of hampering ferroptosis in tumor cells based encompassingmilieu[109,110]. DHFR diminishes BH2 in cells viaimplicatingNADPH , therefore facilitating generation of BH4. In case ofhampering ofDHFR, tumor cells ferroptosisgets facilitatedthrough synergistic actions of GPX4 hampering agents[72].

Thereby the GCH1- BH4- DHFR pathway possesses crucial part regarding controlling equilibrium amongst oxidative injury in addition toantioxidant defense at the time of ferroptosis along with crosstalks with the *System Xc* GSH- GPX4 pathway as well as FSP- CoQ10- NADPH pathway in a synergisticor complementary fashion. Despite, other mechanistic modes as well as plausible therapeutictargets continue tobe estimated, the isolated plausible therapeutictargets mightbeutilizedfor getting chemotherapeutic resistance in case of OC.

**2.3.D. Mitochondrial dihydroorotate dehydrogenase(DHODH) - CoQ10H2 pathway.** DHODH- $CoQ_{10}H_2$ pathway

Themitochondrial DHODH- $CoQ_{10}H_2$ pathway in addition toFSP- CoQ10- NADPH pathway portray thetwo main lipid antioxidant systems in mitochondria. In case of hampering ofone of the systems, the cell generates greater dependance onthe other antioxidant systems, along with once hampering ofbothsystemsoccur ,mitochondrial lipid peroxidation takes place, leadingto ferroptosis[110].

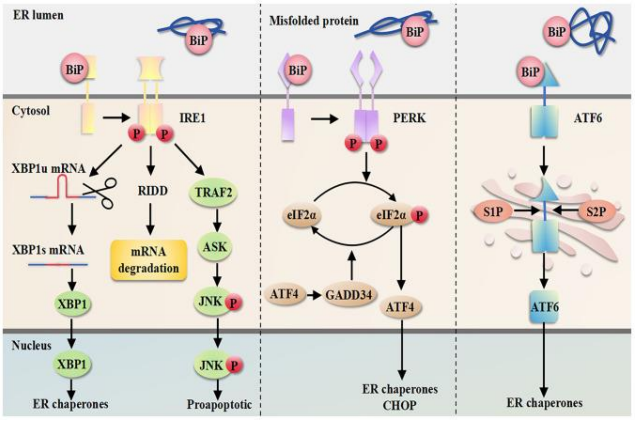
CoQH2, portrays free radicals trapping antioxidantpossessing antiferroptotic actions. DHODH placement is onthe outer surface of innermitochondrial membrane(IMM), as well ashampers ferroptosis by transformation of CoQ10 to CoQ10H2 for diminishing lipidsin mitochondria. Dihydroorotate/orotate/ substratesorDHODHproductssupplementation mitigated/escalated the hampering actions of GPX4 respectively, therebymodulatingcellularferroptosis[111].

The mitochondrial DHODH- $CoQ_{10}H_2$ pathway in addition toFSP- CoQ10- NADPH pathway work independently of each other , however both resulted in reduction of CoQ10 to CoQ10H2 for escalating the mitochondrial defense mechanistic modes against ferroptosis.

**3.ERS**

On getting challenged by inherent factors for instance oncogenic activation, changed chromosome numbers or escalated capability of liberation, along with extrinsic factors for instance deprivation of nutrients as well as acidosis, changed protein homeostasis result in accrual of misfolded in addition to unfolded proteins in the lumen of ER, causing activation ofERS in addition to UPR, therefore restoration of homeostasis in cells[19]. Nevertheless, in case of continuation ofERS/ robust stimuli,UPR threshold getsovertaken, cell demiseresults, which inturn results in cancer generation[112].

Starting of UPR occurs by three main ERS sensors, with their placement in the ER membrane, inclusive of inositol requiring enzyme protein 1α (IRE1α), Protein kinase R-like endoplasmic reticulum kinase (PERK) along with activating transcription factor6(ATF6) [113]. TheER chaperone binding immunoglobulin protein (BiP) works in the form of master controller of the UPR binding as well as inactivating the three ERS sensors, IRE1α, PERK in addition to ATF6[113], negative controlling them along with guaranteeing their inactivating status. Onaccrual ofmisfolded proteins in the lumen ofER ,their binding occurs to the hampering chaperone BiP as well as separate it, activating the three ERS sensors for starting of UPR signaling[114]. Fig2 details ERS.




Legend for Figure2

Courtesy reference no-86Mechanisms of ERS. Accumulation of unfolded or misfolded proteins in the lumen of the ER activates three transmembrane proteins of the unfolded protein response (IRE1, PERK and ATF6) and thereby restores cellular homeostasis. IRE1: Activation of IRE1 kinase results in the excision of an intron in the mRNA encoding the XBP1 transcription factor, and ligase mediates the linking of two mRNA fragments to produce stably active XBP1s. Stable XBP1s activity is involved in subsequent ER biogenesis. PERK: GADD34 forms a loop by regulating eIF2α dephosphorylation, thereby modulating ATF4-mediated ER biogenesis. ATF6: ATF6 is translocated to the Golgi under conditions of ERS and is sequentially hydrolyzed by S1P and S2P proteins, thereby regulating ER biogenesis. ATF4, activating transcription factor 4; ASK, apoptosis signal-regulating kinase; ATF6, activating transcription factor 6; BiP, binding immunoglobulin protein; eIF2α, eukaryotic translation initiation factor 2α; ER, endoplasmic reticulum; ERS, ER stress; GADD34, growth arrest DNA-damage 34; IRE1, inositol-requiring protein 1α; P, phosphorylated; PERK, protein kinase RNA-like ER kinase; RIDD, regulated IRE1-dependent decay; S1P, serine protease site 1; S2P, metalloprotease site 2; TRAF2, tumor necrosis factor





receptor-associated factor 2; XBP1, homeostasis transcription factor X-box protein 1.

**3.1IRE 1 pathway**

IRE 1 constitutedbytwo isoforms-namely IRE1α as well asIRE 1β; IRE 1β expression basically takes place in gastrointestinal Tract(GIT), along with respiratory tract, while IRE1α possesses broader expression[115]. The cytoplasmic tail IRE1α possesses twodomains,a serine /threonine kinase, structural domain in addition to aribonuclease(RNase) structural domain that function in togetherness[116]. Subsequent to binding to misfolded proteins activation ofkinase domain of IRE1α occurs, followed byits going through dimerization, coupling along with the transautophosphorylation, resulting inectopic activation of structural domain ofRNase[117]. With the catalysis of active RNaseexcision of intronwhich possesses26 nucleotides ( nt) frommessenger ribonucleic acid(mRNA) encoding homeostasis transcription factor X-box binding protein 1 (XBP1), subsequently cleavage of two mRNA fragments occurs byRNA splicing ligase RNA 2'3' cyclicphosphate as well as5'OH ligase resulting in formation of active transcription factor XBP1 (alias spliced form or XBP1s) [118]. XBP1sisimplicated in thegenes encoding ER membrane biogeneration, ER proteins folding, ER correlated breaking down, in addition toplethora of UPR [119]. C/EBP-homologous protein(CHOP) ,a controller of ERS stimulated apoptosis,getsactivated by activatingtranscription factor4(ATF4) via PERK- ATF4- CHOP pathway[120]. Additionally, IRE1α facilitates apoptosis by activating apoptosissignal regulated kinase 1(ASK)/ c-Jun-N-terminal kinase(JNK) pathway by binding of tumor necrosis factor receptor associated factor(TRAF) [121]. Furthermore, regulated IRE1-dependent decay of mRNA (RIDD), represents an innovative UPR controlled pathway, which has been isolated in controlling cell fatein the impact of ERS . Activated RNase possessthe capability of targeting mRNAs along with the miRNAs by controlling such pathway[122].

Zundell etal. [123], illustrated that pharmacologicalhampering of IRE1α/XBP1 pathway, might work in the form of an innovative approach for AT-rich interactive domaincontaining protein(Arid1a) mutant cancers as well as XBP1geneKO led to improvementof cellsurvival in case of inactivated ovarian clear cell carcinomas[bearing Arid1a [123]. Song etal.[124], illustrated that regulating ERS or targeting the IRE1α- XBP1 signaling manipulated mitochondrial actions, in addition to therefore regulating T cells metabolic adapting along with tumorigenic capability in casesofOC [124]. The mitochondrial -correlated ER membrane further might work in the form ofa significant association among st mitochondria along with the ER[125]. The continuation of activation of IRE1α- XBP1 pathway of dendriticcells in OC microenvironment was reported by Cubillos Ruiz etal.[126], in view of the sustenance of ERS that interfered with antigen presenting (AP) capability ofmetabolic homeostasis of the dendriticcells as well as reducedtheir protective working in embracingT cells against tumors, emphasizing adistinctimmunotherapeuticstrategyfor OCtherapy. OC cells use ERS for cellsurvival via the activation of IRE1α/XBP1 pathway, amongst rest of pathways as well as coactivator associated arginine methyltransferase 1 (CARM1)that is canonically upregulated in OC cells has been displayed in the controlling of XBP1s target genes in addition to possess selective sensitivity to the hampering of IRE1α/XBP1 pathway, mightbe utilized in the form of aplausible therapeutictarget approach for treatment of cells which expressCARM1[127].

**3.2 PERK pathway**

PERK represents a transmembrane which has a kinness to IRE 1, that possesses ER lumenal dimerization structural domain in addition to acytoplasmic kinase structural domain. The tubulin dimerization structural domain of PERK possesses lesser akinnessto structural domain of IRE 1. The cytoplasmic kinase structural domain of PERK furthergoes via trans autophosphorylation, in reaction to ERS, however it differs fromIRE 1 init further leads to phosphorylationoftranslationalinhibitor eukaryotic initiation factor2 α(eIF-2α),at serine51 along with the phosphorylated eIF-2α hampersfull translation of proteins, as well asdecreases the quantities of proteins gaining entry into theER lumen[128]. Additionally,eIF-2αphosphorylation, changes theeffectiveness of AUG start codon[129], that leads topropensity fortranslation of ATF4 mRNA[128].

ATF4 represents a transcription factor whichactivates downstream UPR target genes, forinstance expression of growth arrest enhanced DNA damage inducible 34(GADD34), that stimulate the expression of CHOP [128,130]. CHOP facilitateDNA injury, hampers cellproliferation in addition to activates apoptosis by upregulatingproapoptotic B cell lymphoma-2(Bcl2) family members[131]. Thereby ATF4 works in the form of a significant factor in ER working gene expression, ERS modulated ROSformation , along with ERSmodulated apoptosis . ATF4 further possesses the capability of controlling dephosphorylation ofeIF-2α via GADD45for generatinga feedback loop for reverting PERKmodulated translation decay[132]. Additionally, PERK phosphorylates nuclear factor erythroid-2-related factor-2(Nrf2), therefore upregulating antioxidants for facilitatingcellular antioxidation[133]. Collectively, these outcomes suggest that PERK-eIF-2α pathway modulates facilitation of cellsurvival at the time of ERS , however switches to the facilitation of apoptosis in case of continuation of ERS as well as aidsin sustenance of cellularhomeostatic equilibrium by activating ATF4 in addition toNRF2. Thereby PERK pathway represents afavourable therapeutic targetfor OC treatment.

**3.3 ATF6 pathway**

ATF6 represents a type IItransmembrane witha carboxy terminal-stresssensing lumenal structural domain as well as amino terminal b Zip transcription factor structural domain[134]. Transportation of ATF6 occurs to the golgi apparatus in case of situations of ERS,where its hydrolysis occurs in a sequential manner by the serineprotease site1(S1P)in addition to metalloprotease site2(S2P) proteins for the liberation ofamino terminal transcription factor structural domain which synergistically with XBP1 resulted in upregulation of genes implicated in proteins folding, along with the ER amplification in addition to genes implicated in ER correlated breakdown pathway constituents[135]. In case of OCtumor tissue it has been displayed that ATF6 expression of OC is greater in tumor tissue in contrast to normal ovarian tissue[136], as well as irreversible ERS,it resultin downregulation of quantities of antiapoptotic proteins [137]. Additionally, by controlling ATF6, sensitivity of OC cells to chemotherapeutic drugs mightbe changed[138]. Nevertheless,part ofATF6 in case of ER cell demise continues tobe uncharted in addition tocotargeting chemotherapeutic drugs for improvementof OCcellsurvival still is uncharted .

**4. Crosstalk of Ferroptosis along withERS** in **OC**

With thesluggish escalation ofattraction in ferroptosis along withERS, escalating quantities of studies have illustrated thatferroptosis along withERS possessa significant influence on OC, with intricate association amongst the two [22,139].

Chen etal. [140], observed thatcontrolling ferroptosis in OCcellsenhanced the anti proliferative actions of cannabinoid derivative in vivo, as well asin vitro efficaciously hampering the generation of OC[141]. Organoids got utilized by Liu etal. [142], where they illustrated that hampering ofovariantumorigenesis occured subsequent toefficaciously targeting ferroptosis. Additionally, ferroptosis associated mechanistic modes hadthe capacity of reverting cisplatin resistance in OC[14], influencing chemotherapy resistance in OCalong with the prognosis of patients withOC[143]. Luo etal. [144], promoted the plausible clinical translation of targeting ferroptosis OC diagnosis in addition to synergistic therapy by combination offer roptosis mechanistic modes with the nanotechnology, magnetic resonance imaging (MRI) as well as cisplatin chemotherapeutic treatment [144].

ERS possessa significant the generation in addition toprognosis of patients withOC.As per studiesactivation of UPR sensorsas well as therefore ERS stimulated possesses the capability of stimulating apoptosis of OC cells [145], in addition to controlling of ERS correlated targetsimpacting resistance to chemotherapy regarding Octherapy [146], emphasizing the plausibility of innovative targets regarding OCtherapy.

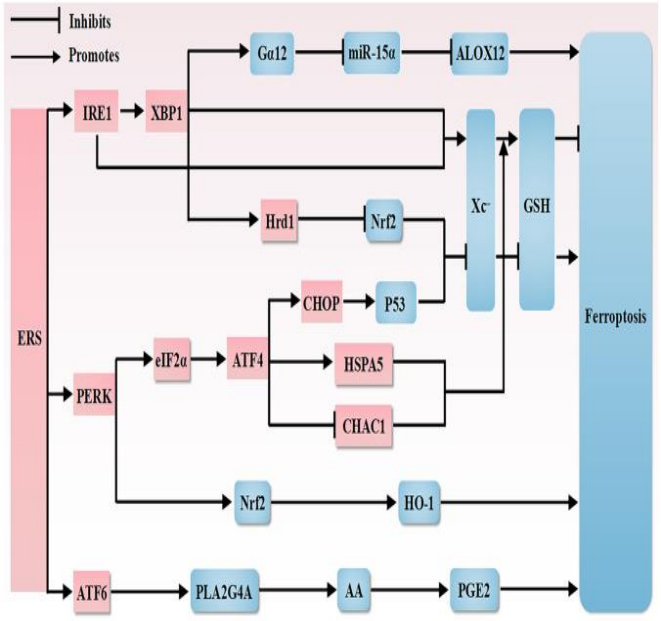
Zhang etal. [147], generated an attractive medical gadget for the prognostic evaluation of OC patients with epithelial OC by generatinga risk classification for the differentially expressed genes correlated with ERS.Ma etal. [148], made use of nanotechnology for precision along withlong lasting stimulating photodynamic reaction- therefore stimulating antitumor actions in case of a mouse model of OC .

An escalating quantities of studies have illustrated the existence of association amongst ferroptosis along withERS, thatshare akin pathways [149], as well asROS,a side derivative of ERS, might aggravate ferroptosis, whereas ERS portrays acritical region at the






time of ferroptosis, further aggravate ferroptosis. Nevertheless, ferroptosis along withERS havenotbeen detailed in togetherness with regards to OC, as well as their crosstalk studies are not present.Figure3 illustrates observed mechanistic modes correlated with ferroptosis along withERS.




Legend for Figure3
Courtesy reference no-86Interactions between ferroptosis and ERS. ERS induces ferroptosis. ERS activates the IRE1α-XBP1s-Gα12, PERK-eIF2α-ATF4-CHOP, PERK-Nrf2-HO-1, PERK-P53-System $Xc^-$ and ATF6-PLA2G4A-AA-PGE2 pathways to induce ferroptosis. ERS inhibits ferroptosis. ERS inhibits ferroptosis by activating the PERK-eIF2α-ATF4-HSPA5 and PERK-eIF2α-ATF4-CHAC1 pathways. AA, arachidonic acid; ALOX12, arachidonate 12-lipoxygenase, 12S type; ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; CHAC1, cation transport regulator homolog 1; CHOP, C/EBP homologous protein; eIF2α, eukaryotic translation initiation factor 2α; ERS, endoplasmic reticulum stress; Gα12, G protein subunit α 12; GSH, glutathione; HO-1, heme oxygenase-1; Hrd1, E3 ligase; HSPA5, heat shock 70 kDa protein 5; IRE1α, inositol-requiring protein 1α; miR, microRNA; Nrf2, nuclear factor erythroid 2-related factor 2; PERK, protein kinase RNA-like ER kinase; PGE2, prostaglandin E2; PLA2G4A, phospholipase A2 group IVA; XBP1, homeostasis transcription factor X-box protein 1.

Zhong etal. [21],illustrated that ERS gets modulated by controlling of ferroptosis,they illustrated that ferroptosis as well asferroptosis modulated ERS resultin injury to prefrontal cortex neurons in addition to ferroptosis in prefrontal cortex neurons thatresultin activation of ERS correlated PERK- ATF4- CHOPpathway. The ferroptosis hampering agents of LOXs forinstance liproxstatin -1alongwith the iron chelator desferoxamine (DFO), diminished the expression quantities of part restoration of ferroptosis correlated protein, upregulation of Nrf2 expression, downregulation of phosphorylated PERK, ATF4 as well asCHOP, in addition todiminished ERS by hampering ferroptosis. This led to mitigation of chronic intermittent hypoxia stimulated neuronal injury along with cognitive impairment , that yielded a therapeutic target with regards to treatment of neurocognitive impairment which occurred as aresult of chronic intermittent hypoxia[21]. ERS works in the form of a significant factor with regards to causative factor for the obesity correlated myocardial abnormalities with the upregulation of ERS markers which occur in case ofcontinued obesity. Tauroursodeoxycholic acid(TUDCA) possesses the capacity of ameliorating obesity correlated ERS stimulated myocardial impairment,whileferroptosis stimulates the depletion of advantageousactions yielded by TUDCA as well as escalates the actions of ERS[150]. Yang etal. [149], observed that activationof ferroptosis signaling in tumor cells facilitated the generation as well asliberation of exosomes which possesses the misfolded in addition to unfolded proteins, hampered ERS along with cellsurvival of the tumor cells[176]. Furthermore,ithas been demonstrated that the ERS-ferroptosis signaling - exosomes pathway stimulated ERS agents resistance ,emphasizing plausibly crucial intracellular mechanistic modes, which mightbe implicated in case of ERS signaling, ERS homeostasis as well as resistance to chemotherapeutic agents in cancer. Dihydroartemisinin(DHA) possesses the capability of stimulating ferroptosis of immunogenic cells in lung cancer, by accrual of LPO in addition to concomitantly stimulate cellular ERS. Greater evaluation illustrated that ferroptosis hampering agents resultedin depletion of DHA stimulated ERS, emphasizing a plausibly innovative therapeutic approach for the cancer therapy with theuse of canonical Chinese medicine in case of cancer immunotherapy[151].

Akin tothat,the controlling of ERS further is capable of influencing ferroptosis. Han etal. [152], demonstrated that the polydatin mitigated early braininjury subsequent tosubarachnoid haemorrhage via upregulation of sirtuin (SIRT1) expression, along with therefore hampering ferroptosis in neuronal cells[152]. Wang etal. [153], displayed that ERS hampering agent 4phenylbutyric acid hampered ferroptosis inepithelial cells in theairway for the avoidance of acute lung injury, by ERS downregulation, reverting the lipopolysaccharide(LPS) stimulated reduction in GSH as well astherefore hampering the of ferroptosis proteins, ACSL4,COX2 in addition to ferritinheavy polypeptide(FTH1), therefore emphasizing plausible modalitiesfor the acute lung injury.I*n vitro*workon ovarian granulosa cells displayed escalated ROSformation, lipid peroxidation along with intracellular iron quantities in cells getting testosterone(T) therapy. Theexpression quantities of SLC7A11, a crucial protein of *System Xc.* $^-$ were further changed,leadingto diminished intracellular GSH generation as well as cystine insufficiency, which resultedin reduction of intracellular GPX4 quantities, the basic intracellular antioxidant, therefore stimulating ferroptosis in granulosa cells. Nevertheless, the T stimulated ferroptosis event gotdiminished by the ERS hampering agents [154]. Jiang etal. [155], observed that IRE1α, a controlling protein which works in the form of a significant factor with regards to UPR, estimate the proneness to ferroptosis by controlling the generation of GSH , pointing that hampering of IRE1αis an attractive approach for mitigating ferroptosis correlated pathological disease.Additionally,it wasillustrated that exogenous melatonin,the way elaborated by usearlier innon-alcoholic fatty liver disease (NAFLD) treatment[24], works by hampering ERS through the MT2/cAMP/PKA/IRE1 signaling pathway[156].The heavy metal cadmium works in the form of an escalated risk factor regardinghepatocyte ferroptosis as well as liver damage in addition to ferroptosis development is usually associated with activation of PERK-eIF-2α- ATF4- CHOP pathway,whose countering mightbe attained by hampering of the ERS fordiminishing ferroptosis-thus cadmium stimulated ferroptosis is basedon ERS[157]. Cadmium further controls ferroptosis along with stimulates nephrotoxicity in renal tubular epithelialcells via the above-mentioned mechanistic modes causing kidney injury [158]. Results obtained from Ulcerative colitis (UC) studypointed that ERS implicatedin the generation of ferroptosis. eIF-2α portrays a constituent of PERK branch of the ERS reactions, along with thephosphorylated nuclear factor κB(NFκB)p65 hampers ERS, therefore conferred protection to the intestinal epithelial cells in UC by directly crosstalking with eIF-2α[159].
Colorectal cancer (CRC)portrays a frequent malignancy of the digestive system, where primary surgery, along with chemotherapy had restricted efficaciousness[160].Tagitinin C, portrays a naturalproduct, stimulates ERS generation, resultingin nuclear translocation of Nrf2 in addition toupregulation of hemeoxygenase-1(HO1). HO1 portrays a downstream effector of Nrf2, which resultsin escalatedpool of unstable iron, therefore facilitating lipid





peroxidation.A synergistic antitumor action of escalated pool of unstable iron with erastin resultedinstimulating ferroptosis in CRC cells . Therefore tagitinin C has been isolated in the form of an innovative stimulator of ferroptosis along with robust sensitizer[161]. Additionally, in case ofprostate cancer study, the modulation of arachidonic acid (AA ) liberation as well asbiogeneration of prostaglandins,ATF6 , PhospholipaseA2 GroupIVA was observed to confer protection to the prostate cancer cells from ferroptosis[162]. Upregulation of Gα12via IRE 1-XBP1 pathway subsequent toERS in hepatocytes , thus facilitatedthehepatic ferroptosis as well asaggravates acute liver injurythrough Rho associated coiledcoil containing protein 1 (ROCK), modulated 12lipooxygenase( ALOX12) in addition tomiR-15a [163]. Additionally, in case of a studycorrelated with diabetic nephropathy, ERS resultedin downregulation of SLC7A11 expression via the XBP1- E3 ubiquitinligase- Nrf2pathway, which diminishedGSH antioxidant quantities in addition to escalated cellular sensitivity to ferroptosis, therefore stimulating ferroptosis, which yielded understanding into the plausible mechanistic modes which postponed epithelial –mesenchymal transition (EMT) in renal tubular cells[22].

Additionally, variable studies have illustrated herbal constituents are capable of causingimprovementof ferroptosis by modulating ERS. Esculin,a substance which is an extract from cortex of willow bark, hampers the generation along with thepropagation ofcolon cancer, by activation of ERS -PERK signaling pathway as well asstimulating apoptosis in addition toferroptosis via the Nrf2/HO-1 along with the eIF2α/CHOPpathways[164]. Tanshinone IIA, the basic active constituent of the canonical Chinese medicine,Danshen, has been illustrated to execute antitumoractions basically in theER modulated ferroptosis signaling pathway, causing downregulationof ferroptosis in tumor cellsvia PERK - ATF4- heat shock 70kDaprotein5( HSPA5) pathway[165]. Escalated acetaminophen dosage, is the main etiological factor of drug stimulated acute liver injury .Salidroside hampers ERS modulated ferroptosisthrough the ATF4- cation regulator homolog-1axis by activatingthe 5' AMP-activated protein kinase(AMPK) /SIRT1 signaling pathway as well as possessesa significant partin attenuating acetaminophen stimulated acute liver injury[166]. In case of astudy on glioma,DHA stimulated ERS resultedinupregulationof ATF4through PERK by escalatingthe expression in addition to actions of GPX4,thushampering DHA stimulated lipid peroxidation along with conferred protection to glioma cells throughuse of via PERK/ATF4/HSPA5 pathway , emphasizing an innovative mechanistic modes for glioma therapy [167].

Additionally, ERS stimulates $Ca^{2+}$ liberation as well as transportation of TF gets controlled by cytoplasmic $Ca^{2+}$ quantities therefore influencing intracellular iron quantities as well as ferroptosis in colon cancer cells[168]. Ferroptosis treatment which concentrates on intracellular escalated ROS generation in addition to LPO accrual,has proven to be an innovative approach for lung cancer therapy .Administrationofaferroptosisnano-stimulator, constituted of DHA in addition to pH reactive calcium phosphateis doneto lungs using a nebulizer. The cyclic $Ca^{2+}$-burst possesses the capability of modulating ERS , thereforefacilitating ROS accrual, resultinginaggravation of ferroptosis, yielding aninnovative research trajectoryfor lung cancer therapy[169].

It has been illustrated thatferroptosis along withERS, are further associated with tumor angiogenesis. In case of a study associated with glioma, escalatedATF4 expression, that represents adownstream transcription factor , activating downstream target genes of UPR,facilitated angiogenesis by promoting tumor shaping of the vascular structures in *System Xc.* ⁻ dependent fashion along with erastin-anacknowledgedstimulator of ferroptosis as well as RSL3(,a GPX4 hampering agent) hadthe capacity of diminishing ATF4 stimulated angiogenesis[170].

In reference to the generation of innovativeagents researchers on naturalsubstancesin addition to their derivatives, represents a favourable idea in generation of innovative treatments for cancer.The inimical sequelae have to be taken intoaccount as well as off-target effects which the capacity of negatively influencing quality of life (QOL) of patients. Agents that have escalated sensitivity as well as specificityare required to be formed guaranteeing least off-target effects in addition toplausibletoxicities[171]. Various studies have illustrated thatdiminishingoff-target effects possess the capacity of improvementof outcomes as well as prognosis forcases of OC& are robustlyassociated withferroptosis along withERS[172]. Dahlmanns etal. [173], observed that adjusting the mechanistic modes of ferroptosis caused improvementof tumor treatment[173], however disrupting ferroptosis induction resultedin forming off-target effects, therefore diminishing therapeutic effectiveness [173]. Akin to thatithas been illustrated that, ERS mightbe implicated in modulatingoff-target effects in case of glioblastomamultiformes[174]. ConsistentlyROS hampering agents, that are intricately associated with ferroptosis along withERS, possess certainmagnitude of impacting off-target effects[175]. Advancementsdone recentlyin conjugate drug deliverysystem[176],liposomal formulations[177], nanotechnology[178], combined with bioactive agents for the broader disease kinds for instance cancer might resultin improvementof effectiveness via localized administration along with exactitude delivery resultingin avoidance of off-target effects. Collectively, these suggest that ERS crosstalks with ferroptosis via, signaling pathway, controlling proteins, as well asassociated factors, emphasizing plausible target in addition tofor the avoidancealong with the treatment of disease .Nevertheless, exactitude mechanistic modes of howERS crosstalks with ferroptosis continue tobe uncharted for generating therapy the avoidancealong with the treatment of disease .

## 5. Conclusions along with furtherDirections

Ferroptosis along withERS, have gradually emerged in the form of favourable strategies for researchers, where studies have illustrated that ferroptosis along withERS, are associated with generation in addition toplausibilityof therapyof gynaecolgical malignancies[7,9,19,179]. OCthathas maximum mortality rates of gynaecolgical malignancieshas evoked considerable interest: Nevertheless, no germanework withregards to plausible mechanistic modes of crosstalkamongst ferroptosis along withERSexists.Here in thisreviewwe focus onpathogenesis of ERS as well as ferroptosis along with frequent signaling pathways in OC in addition to thecorrelatedpathways inlung, liver as well asCRCwith the objective of yielding innovative approaches forthe therapy for the avoidance,andprognostic asssessment along with OC treatment.

Aplethora of studies[180-182], have illustrated that ERS as well as ferroptosis work in the form ofplausible therapeutictargets for the avoidancealong with the circumstances in addition to generation of OC, along with the prognostic asssessmentin case ofpatients with OC, whereas combination with other agents along withinnovative approaches further yieldedacquiring therapeutic actions, given innovative fields on OCresearch. Particularly, proliferation as well as the growth of OC cells controlling the ironquantities in OC cells, therefore ferroptosis in OC cells,mightbe stimulated inOC cells [89], which influences the circumstances in addition to generation of OC.Furthermore, ferroptosis induction plausibility mightbe attained in OC cells for the tackling of chemoresistance [183]. ERS possesses the capability of hampering cell proliferation in addition to generation of ferroptosis by controlling the germane pathway[184], capable oftargeting OC cancer cellswith chemoresistance ,in addition to ERS stimulated apoptosis has been displayed to resultin improvementofsensitivity of the cancer cells to paclitaxel, therefore prognostic improvement of OC patients[185].






Furthermore, existence ofa correlation amongst the two,is there with ERS stimulating ferroptosis, resultingin Fe $^{2+}$ accrual along with lipid peroxidation via correlated pathways [168], as well as ERSwhich possesses greater than 50% of full lipid bilayers in case of a particularcell,that is thelipid source formost of cytosolic membranes, therefore are crucial for the startingof ferroptosis[186]. Ferroptosis possesses the capability of sustenance of ER homeostasis by signaling in addition tocontrolling the magnitude of ERS. Ferroptosis is capable of further gettingpositivelycontrolled bystimulating ERS via variable pathways .

Nevertheless, ferroptosis as well as ERS possess variable complicated natureof mechanistic modes in addition toplethora of innovative mechanistic modes, signaling pathwaysalong with plausible therapeutictarget are getting unraveledcircumspectly, there is plausibility that numerousmore are awaitingto getunraveled. For instance theaforementioned fourmechanistic modes described, pathways correlated with lipid antioxidation in case of OC specifically GCH1- BH4- DHFR pathwayas well as DHODH- $CoQ_{10}H_2$ pathway still continue tobe uncharted. Mitochondrial OS isintricately correlated with associated events in ferroptosis as well as ERS in addition to insight withregards to mechanistic modesfor mitochondria are currently missing**.** Additionally, earlier initiating OC is pernicious in nature along with mechanistic modesregarding diagnostic preciseness, insufficiencyof work on iron quantities amongst OC tissues at the time ofvariable stagesofnormal ovarian tissues,however as per Basauli etal. [43],in case of HGSOC'S there is existence of diminished quantities of FPN(the iron exporter) whereas escalated quantities of TFN1(the iron importer) implicated in greater tumor iron quantities resultingin greater tumor proliferation as well as invasion and diminishing iron quantities reverts this tumor proliferation,called ironaddiction by them,however greater studies have to replicatethe same[43]. Disruption of iron metabolism at the time of OC might further hamper further propagation of OC[89]. Circumstances, propagation along with treatment of OC represents a complicated event, as well as a complicated association is existentwith ERS in addition toferroptosis.If there is existence of the germane pathways asin other diseases possess commensurate part inOC, along with if clearcut variations in part in variable cells at variable stages of OC as well as if they possess proportional controlling part in circumstances, development along with recurrence has to be estimated. Moreover , prognostic anticipation of OC has too many inadequacies without clinical endorsement. Despite, present studies withregards to variablediseases have illustrated interactions amongst ferroptosis as well as ERS possess a germane improvement actions on the diseases [21,187-189], even now there is absence of germaneresearch in the context of mechanistic modes on the manner interactions amongst ferroptosis as well as ERS occur in OC.

Dependent on the acquisition of greater insight withregards to plausible therapeutic targets of ERS as well as ferroptosis, the part of mechanistic pathways in the events of OC, the influence of interactions amongst the two, the mannertranslation of the outcomesobtained from workdone, with existence of plenty of botherationsin translatingclinicalexperimentaloutcomes in clinical scenario. In reference to clinicalindex determination theuseof above-mentioned mechanistic modes in addition torecent advancements in scientific technology, for instancenanomaterials ,MRI,XRays might in combination aid in early pick up ofpathological factorseven prior to initiation of OC along with evaluationof the effectiveness of or prognostic asssessment at the time of treatment initiation or subsequent to disease therapy . Evaluationof quantities of iron metabolismat the time ofgermane investigations, might aid in early pick of OC , with plausibility of causing improvementof treatment choicesin addition toresultsfor the patients with OC .Thetrajectoriessuch studies takeare awaitingclinicaltranslation. Therefore,extra screening of frequently utilized chemotherapy regimensIn reference to developmentof innovative agents have clearcut safety as well as tolerability botherations apart from generation of chemotherapy resistance. Therefore screening of innovative agents that are safe andtolerable is theneed of hour.If ERS hampering gets utilized clinically is awaited. Additionally, different studies have observed that canonical Chinese medicine[65,165-,190], have efficaciousness in the controlling of interactions amongst ferroptosis as well as ERS in OC, therefore, clinical safety assessment is mandatory. Thereby, an exhaustive explorationof these is required to see if combo would be synergistic along with hamper resistance development needs to be seen.

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