SOURCES OF ROS SPECIES AN ITS HARMFUL AND BENEFICAL EFFECTS ON HUMAN HEALTH

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Abstract

When the antioxidants in our immune system cannot neutralize or convert Reactive oxygen species into safe molecules at the rate at which it is produced then this imbalance is termed as "oxidative stress". It is related with a wide array of diseases that includes cancer, diabetes, cardiovascular diseases, hypertension etc. These ROS species however are utmost essential for functioning body which the proper of human are produced as a consequence of partial oxidation of cellular metabolism performing essential functions such as protein phosphorylation, activation of several transcriptional factors, apoptosis, immunity, and differentiation. The sources by which these are produced can be broadly classified are intrinsic and extrinsic sources. There are variety of natural antioxidant enzymes of human body that combat against this oxidative stress. The extrinsic sources of ROS include the use of natural plants, extracted flavonoids and vitamins. In this review we will briefly explain how the sources of ROS, its essential function in human body, its elevation and associated damage to organs and effect on various diseases, and a hope of finding a way of how this oxidative stress can be exploited for therapeutic potential.

Keywords : ROS , sources of ROS, oxidative stress, ROS and cancer

1 Introduction

(i) (ii)

Reactive oxygen species (ROS) or oxidants are oxygen containing free and non-free radical molecules. Commonly defined ROS are superoxide anion $(O2^{\bullet})$, hydroxyl radical (HO $^{\bullet}$), peroxyl (RO2 $^{\bullet}$), alkoxyl (RO $^{\bullet}$) radicals, Hydroperoxyl radical (HO2 $^{\bullet}$) and oxygen derived non radical species including hydrogen peroxide (H2O2), Peroxynitrite (ONOO⁻), Hypochlorous acid (HOCl⁻), singlet oxygen (1O2) and Ozone (O3). (8, 9) These ROS species are produced as inevitable byproduct of aerobic metabolism like cellular respiration, photosynthesis etc. and exposure to xenobiotics. (10, 11). A large number of essential life processes inside the cell are dependent on production of ROS and are essential for its proper functioning. These include protein phosphorylation,(12-14) activation of several transcriptional factors,(15-17) apoptosis,(18, 19) immunity, and differentiation. However all these ROS share a common characteristic of causing an oxidative damage to biological molecules such as lipid(20, 21),

protein(22) and DNA(23-25) when its production is increased above a normal level causing an oxidative stress. High doses of ROS can even lead to direct cell death or apoptosis. Low doses are however essential for cellular activation, cell proliferation, intracellular cell signaling(26, 27) etc.

Some of the Intracellular endogenous sources of ROS are mitochondria,(28, 29) NADPH, (30-32) Prostaglandin H Synthase (PHS), cytoplasm, lysosome, Microsome I and II. (33) Some of the exogenous sources UV light, x-rays, gamma rays, any chemical that result in peroxide and superoxide formation or metabolized to form radicals such as Ozone, singlet oxygen Quinones, nitroaromatics, bipyrimidiulium herbicides, polyhalogenated alkanes, phenols and aminophenols , Chemicals that release iron (ferritin).(34, 35)

Electron transport chain (ETC) allows to H+ gradient across inner membrane of mitochondria which leads to the formation of ATP. However, it also forms ROS as a byproduct. In ETC high energy electrons are produced by creating NADH and FADH2 molecules and using these electrons to create a proton gradient. The final step in ETC is the acceptance of these electrons by oxygen. A total of 4 electrons and 4H are combined with oxygen to completely reduce this oxygen to water. However, under certain conditions if oxygen only partially reduces by accepting one electron then it forms superoxide, acceptance of two electrons results in the formation of peroxide. These are reactive species which upon reaction with nucleic acid or protein disrupt their normal functioning. Our immune system act against these ROS species by producing vitamins of esp. C and E type and protecting antioxidant enzymes such as superoxide dismutase, peroxiredoxins, glutathione peroxidase and catalase. Normally complex IV (cytochrome oxidase) of ETC has a tight hold of oxygen and its derivatives therefore the formation and rummage of ROS are in coherence. When the antioxidants in our immune system cannot neutralize or convert these ROS species into safe molecules at the rate at which it is produced then this imbalance is termed as "oxidative stress". Such an imbalance is produced when inflammatory phagocytes are exposed to foreign agent or when prooxidant xenobiotics such as CCl4 and paraquat enter the body. DNA, protein and lipids are attacked by ROS to cause damage. This review will briefly describe the ROS generation by various endogenous and exogenous sources including the beneficial as well as the potential damage that can be caused by these oxidants. (36)

2 Exogenous and Endogenous sources of ROS

2.1 Endogenous sources

2.1.1 Mitochondrial formation of ROS

In mammals ROS originates from ETC in the inner membrane of mitochondria (mROS) during oxidative metabolism, contributes in redox cell signaling and are important in maintaining cellular oxidative homeostasis and propagation of cellular signaling pathways. Partial reduction of singlet oxygen results in superoxide and peroxide formation which are together termed as mROS. Mitochondrial dsy-functioning results in variety of physiological disorders including neurological disorders, cancer and cardiovascular malfunctioning. Besides its well-known function as a power house of the cell which hydrolyze the phosphate bond of ATP to ADP producing energy, it has key involvement in calcium signaling, heme and steroid synthesis, controlling membrane voltage, multiplication, cell death and keeping balance of reactive species. ETC and TCA are enzymatically controlled reactions. Of wide range of enzymes involved in the

oxidative metabolic process of mitochondria, magnesium superoxide dismutase (MnSOD) is one of them. It prevents the oxidative damage to mitochondria by the conversion of H_2O_2 from superoxide anion, produced during partial reduction of molecular oxygen to OH radical, by Fenton reaction. superoxide dismutases (SODs) is another enzyme which perform the same function and is present with in mitochondria and its cystol. Complex I, II , III, IV of mitochondria are responsible for superoxide oxide formation . These complexes of ETC prematurely brings reduction of oxygen to superoxide radical. I and II complex of mitochondria release ROS into its matrix while the III release into its inner membrane. The ROS in intermembrane space of mitochondria can easily move to cystol than ROS present in matrix. Outermembrane, inner membrane, intermembrane space and matrix all produce ROS but the proximal ROS is produced by the inner membrane of mitochondria. (37)

Complex I and III produce superoxide which diffuse upto 80% in intermembrane space of mitochondria while the remaining is transported by outer membrane of mitochondria utilizing its permeability transition pore (MPTP) to the cytosol. The antioxidant system of body act against this superoxide by making using of enzymes Cu/ZnSOD, MnSOD which dismutate it into less dangerous. Glutathione peroxidases (GPxs) convert H2O2 to water.(38) This H2O2 pass through cellular membranes through quaporin-8 of inner mitochondrial membrane. (figure 1) Internal and external stimuli can both produce these ROS species. Complex enzymes system constitutes in the oxidative stress organelle, mitochondria. Oxidative stress is the redox alteration of ROS species and the disability of bodies' antioxidants systems to work against it. Oxidative stress widely known to be involved with various cancer types and with it being the driving force of cancer pathophysiology. (39) This imbalance of ROS in can be decreased by exogenous antioxidant agents such as tripeptide glutathione, the polyphenolic flavonoids and essentially important micronutrients, for example vitamin A, C and E. Body has the natural ability to combat against this induced oxidative stress and it deals with the help enzyme systems. Some of these enzymes are superoxide, catalyse and enzymes of glutathione system. Superoxide dismutase (SOD) by the use of cofactors of cupper, zinc and iron converts superoxide into oxygen and hydrogen peroxide. Catalyse convert H2O2 into O2 and H2O. H2O2 is reduced by Peroxiredoxins a type of thioredoxin (Trx). The cysteine residue of Trx when active scavenges ROS and keep the protein in its reduced form. Thioredoxin reductase (TrxR) takes electron from NADPH and generates Trx. Glutathione system has a role in maintaining the redox hemostasis by either directly reacting with them or by using cofactor. Glutathione (GSH) is an abundant antioxidant synthesized by cells acts as antioxidant protective mechanism opposes oxidative stress by reducing the disulfide bond formation in protein of cytoplasm. Glutathione peroxidase (GPX) attacks H2O2 and regenerates GSH. The combining of GSH to a number of electrophilic molecules is eased by GST with its level being observed high in different types of cancers and plays a significant function in chemo resistance (figure 1). This natural antioxidant system maintains the redox hemostasis by keeping the optimum ROS level. The dys functioning of genes of antioxidant system will put damage to the important biomolecules such as protein, bring about lipid peroxidation and disrupt the functioning of genetic material along with severe damage to cell and alteration to associated abnormalities in chromosome .(40)Besides the above mentioned internal sources or the endogenous sources some other sources include enzymes and complexes such as NADPH oxidase (41, 42) Hemeprotein complex P450 enzymes, and an enzyme required for oxidation of hypoxanthine and xanthine oxidase. Different metabolic pathways of Peroxisome also generate and regulates ROS species such as OH, superoxide and H2O2 which helps in the cell signaling network and cellular redox metabolism. (43-45)



Figure I Intrinsic source of ROS and its conversion by antioxidant system of body

2.1.2 NADPH

The proteins of NADPH oxidase family have the ability to catalyze a biological reaction by making it possible to transfer the electron from NADPH (nicotinamide adenine dinucleotide phosphate) to 102 resulting in hydrogen peroxide formation. It also produces O2•–. There are 5 homologues of NOX family namely NOX1, NOX2, NOX3, NOX4, NOX5 and two enzymes DUOX1 and DUOX2. These proteins have intrinsic unique features which enable them to be dependent on other components for its enhanced enzymatic action, distribution of a substance to body tissue, regulation of its gene and protein expression and physiological functions. The 1 and 2 type are assumed to be a source of ROS production. (37)

3 Effect on Human health

As mentioned, oxidative stress can damage cellular processes which negatively affect human life. Some of the adverse effect of increased ROS and its subsequent oxidative stress is given below:

3.1 Cancer and ROS

3.1.1 Breast Cancer

Anticancer drugs cause DNA damage which induce expression of anti-apoptotic proteins such as NFkB, thus subsequently decreases the effectiveness of that drug against chemotherapy. ROS generating agents tend to disturb the bearable limit of ROS of cancer cells which will eventually lead to its apoptosis which is dependent on continuous activation of pro-apoptotic MAPK pathways mainly through alteration of activities of mitochondrial pro- and anti-apoptotic proteins by phosphorylation events. The generation of ROS and the initiation of programmed cell death is usually accompanied through ROS-MAPK pathway. The production of ROS also activates a wide range of anti-apoptotic factors such as NFkB that lessens the toxicity of cells promoted by ROS. Between ROS-MAPK pathway and NFkB, targeting both pathways may be beneficial anticancer agent. Agents that can concurrently trigger ROS-MAPK pathway that favors apoptosis and hinder the pathway that acts against apoptosis initiated by ROS then that agent can enhance BC chemotherapy. Disulfiram (DS), a copper dependent molecule is an efficient ROS initiator and blocks the activity of NFkB pathway. ROS activates NFkB which inhibit ROS and JNK pathway, activation of p38 protein and the apoptosis induced by ROS. BCCs have significantly elevated level of NFkB activity. The DS/Cu blocked these functions in cell lines by inducing apoptosis as well as ROS production and its ROS-NFkB pathway. Colony formation was decreased or completely removed while the ALDHbVE and mamosphere was also inhibited. DS/Cu acts on CSCs by decreasing CD24Low/CD44 (46). Arctigenin (ATG) induce apoptosis through caspase independent pathway of mitochondria in MDA-MB-231 by increasing ROS formation via increasing interaction of p22phox/NADPH oxidase 1. This causes ROS to activate p38 MAPK pathway(47). Surfactin is cyclic lipid connected to a peptide and formed by hay bacillus or grass bacillus. It initiates apoptosis in MCF-7 cells by production of ROS. It induces phosphorylation of ERK1/2 apoptosis via triggering and JNK mediated bv mitochondrial/caspase pathway.(48) Chimaphilin extracted from pyrola induce cell death in breast cancer cell line MCF-7 by ROS formation and dysfunctioning of MMP through mitochondrial pathway(49). Glycyrrhiza uralensis extract licochalcone A promoted autophagy and elevated ROS formation for increasing extrinsic and intrinsic apoptosis in MDA-MB-231 breast cells. It also suppresses cancer cell invasion and migration by phosphorylating ATK and the MAPK signaling pathway, (50) Antidepressent paroxetine induced apoptosis of BC MCF-7 cells bv extracellular Ca2+-and p38 MAPK-dependent ROS generation(51)Tetrabromobisphenol A bring about apoptosis in MCF-7 cells by MMP-9 release using MAPK and Akt pathways dependent on ROS.(52)

An antibiotic doxycycline lessen the activity of aldehyde dehydrogenase-positive (ALDH+) isoenzyme which is a characteristic of breast cancer stem cells (BCSCs), HER2+ (human epidermal growth factor receptor 2) and triple-negative breast cancer (TNBC).(53) It also reduce ROS level and the p38 MAPK pathway. The inhibitor targeting this pathway reduced ALDH+ cells proposing a possible role of p58 in supporting BCSCs. The mitochondrial characteristics of stem cells differ from that of non-stem cells. The doxycycline blocks the regeneration capacity of Breast cancer stem cells (BCSCs). It can transition between two phenotypic states, Epithelial-like state (E) characterized by the expression of the CSC marker aldehyde dehydrogenase (ALDH) and the quiescent mesenchymal-like state (M) characterized by the expression CD44+/CD24-. Using four different BC cell lines in which BT474 and SK-BR-3 are HER2+ comparatively has higher frequency of ALDH+ epithelial-like BCSCs while SUM159 is a Claudin-low TNBC cell

line has higher frequency of M bulk tumor cells that are also CD44+/CD24-. SUM149 is a basallike TNBC and has both ALDH+ and CD44+/CD24- BCSCs thus the latter cell line was found to be suitable for experimental determination of doxycycline and its effect on ALDH+ and CD44+/CD24- BCSC populations. The result demonstrated that doxycycline inhibits ALDH+ BCSCs by blocking the formation of ROS as well as that of p38 MAPK signaling pathway(54). Also there is a report suggesting that these E and M phenotypes are favored by metabolic switch to glucose metabolism in basal BC resulting in decreased ROS.(55)

ER+, HER2+ BCSCs display plasticity that enable them transform between 2 phenotype states. This transition allows them to initiate and grow primary tumor. EMT carry cancer cell metastasis and spreading while MET handle colonization and proliferation. Therefore, to treat BC, therapeutics have to target both transition states. The required attributed metabolic changes in M and E CSCs may contribute to resistance of cancer to glycolytic inhibitors. M and E CSCs have different responses to oxidative stress which is associated with its metabolic pathway and redox potential. Metabolic vulnerabilities of these states is exploited by blocking both of antioxidant and glycolysis pathway which can be brought about by thioredoxin-Nrf2, GSH. With this co inhibition tumor growth was found to reduced along with metastasis and tumor initiating capacity.(56)

Rhenium(I)-diselenoether complex (Re-diSe), a drug induced apoptosis against hormone independent breast cell MDA-MB231. A decrease in ROS formation along with various transcription factors TGF- β 1, VEGF-A, and IGF-1 in medium culture containing cancer cells was observed upon exposure to the complex compound. (57) The study showed the significance of these compounds as an anticancer and as an antioxidant agent against the cancer cell line which also exhibited a reduction in ROS level in cancer cells as compare to that of normal cells. The complex was found to be more effective than its corresponding ligand. The underlying mechanism was thought to be attributed to the antioxidant effect of the complex on the aforementioned markers of signaling pathways. It also has the potential to bind its Re atom to one or two guanine bases of DNA. This binding will have effect on the ROS and RNS production by mitochondrial DNA.(57) Re-diselenoether give mono- and bis-guanine Re adducts, which is assumed to damage the crosslinking within same strand of DNA. (58)

Arsenic sulphide regulates expression of proteins of BCSs which can result in the cell cycle arrest at its G2-M check point. It also activates the expression of caspase-7 and caspase -8 which initiates apoptosis in these cells along with elevation of B-cell lymphoma 2 (Bcl-2)-associated X protein/Bcl-2 ratio and reducing the protein expression of anti-apoptotic B-cell lymphoma extra-large. The autophagy also occurs which is shown by the accumulation of protein that are associated with microtubules. It also resulted in the increased intracellular accumulation of ROS in BC cell lines which may aid in increasing metastasis and reducing the growth of cancer. The study thus suggests the arsenic sulphide acts as an anti breast cancer agent by inducing apoptosis through both of its pathways i.e extrinsic and intrinsic , arrest the cell cycle at its phases, induce autophagy regulates protein expression of metalloproteinase-9 (MMP-9) and its signaling along with the production of ROS.(59)

In BC Notch signaling pathway is also involved. Sibilin downregulates the overexpressed Notch-1/ERK/Akt Signaling by the use of ROS and kill the cancer cells of two breast cancer cell lines MCF7 and MDA-MB-231. (60)

The use of natural compounds and its analogues to treat cancer has been in practice for a decade. One such compound is Salvianolic acid B (SB), a large compenent of Chinese herb called Salvia miltiorrhiza is effective against MCF-7.(61) Tinospora cordifolia is a shrub mostly commonly known as heart-leaved moonseed. The medicinal plant has been purified to extract a constituents Bis(2- ethyl hexyl) 1H-pyrrole 3,4-dicarboxylate (TCCP) that acts as effect anticancer agent for MDA MB-231. It does so by generating ROS species and bring about intrinsic apoptosis and restoring the loss of antioncogene function of P53 induces phagocytosis apoptosis in vivo thus results in reduction of cancer multiplication. The purified compound TCCP when administered to the cancer cell lines exhibit an increased ROS and intracellular Ca2+ can cause oxidative stress and regulate apoptosis. The mutated P53 has a suggested role as a tumor promoter helping in its progression survival and making the cancer cells sensitive to respond to chemotherapy. The conversion of it into its wild form is a novel strategy which initiate apoptosis. The TCCP did not change the mutant p53 expression however it persistently elevated the level of phosphorylation (serine15) of p53. The use of blocker to inhibit p53 showed that the TCCP effect was reversed by the inhibitor and promoted apoptosis induced cell survival by mitochondrial apoptosis pathway.(62)

Radiotheraphy increases ROS production with inhibition of cancer cells proliferation and lead to death of normal cells. Cordycepin is a natural compound isolated from fungi with significant antitumor activities against breast cancer. Under oxidative stress Nrf2 reduces ROS elevated level by down streaming genes responsible for it with potential to induce carcinogenesis. Nrf2 regulates various genes linked with oxidative stress. Its stability and level are controlled by various proteins. Overexpression of Nrf2 in response to HER2 is through direct protein interaction and the development of chemoresistance of cancer cells to therapeutic drugs is also thought to be due to this nuclear factor activation. Treatment with cordycepin make the BCCs sensitive to chemotheraphy irradiation through ROS production, HO-1 activation and Nrf2 upregulation. Two BC cell lines were irradiated and treated with the compound resulted in restoration of cell proliferation after irradiation along with promotion of G2/M arrest and apoptosis. The cell lines also possessed higher ROS level and smaller number of γ -H2AX foci. It downregulated/decreased the expression of Nrf2 and HO-1 making it a potent radiosensitizer against Breast cancer (63, 64).

The use of nanoparticle (NP) as a therapeutic approach to treat cancer is now widely in practice. One such effort in this regard was by using Bi2O3 NPs on MCF-7 cells. The cytotoxicity was suggested to be because of oxidative stress which was generated by the NP in response to production of ROS along with oxidative degeneration of lipids and decreased enzyme activities of glutathione (GSH) and superoxide dismutase (SOD)(65).

3.1.2 Liver Cancer

Herbal and natural antioxidants to treat oxidative stress is in clinical trial esp. for medicinal plant that contain phytoconstituents that can act against this stress and also plays a role in redox signaling. (66) Thymoquinone (TQ) is a bioactive compound that has been isolated from plant *Nigella sativa* oil. The obtained compound effect the expression of non- coding liver MicroRNAs (miRNAs), by dysregulating it, causing oncogeneses. The miR-206 increased expression result in different types of cancer including liver cancer (LC). However, its high-level causes metastasis, and promotes apoptosis. miR-206b-3p is a homologue of miR-206 in mice was found to be downregulated by TQ

administration along with decrease of oxidative stress in liver tissues of mice.(67) Chrysophanol, a Chinese herb used against J5 human LC cell line increased ROS formation and cytosolic Ca⁺² levels and decreased membrane potential with induction of necrosis. This necrosis was found to be stimulated/driven by ROS production(68) shikonin induced ROS mediated apoptosis in Huh7 and BEL7402 HCC cell lines with downregulation of Akt and RIP1/NF- κ B activity. (69) Compound of boehmeriasin A series decreased the cell viability of fully differentiated LC cell line and induced apoptosis determined by Annexin V and Hoechst staining via ROS generation by decreasing Akt protein phosphorylation.(70)

A primary liver cancer Heptocellular carcinoma (HCC) is caused by dysregulation autopathy and Nrf2 pathway activation with a relation to oxidative stress pathways. There are reports suggesting the dual role of autopathy acting as antagonizer of tumor cell, however once the cancer progresses it protects death of liver cancer cells induced by various stimuli including oxidative stress. Recently there was found to be physical association between protein adapter p62 of dsyfuntional autopathy and Nrf2 inhibitor, which resulted in increased stability and activity of Nrf2. Pharmaceuticals thus try to develop drugs that target Nrf2-p62 in HCC for the possible cure of liver cancer(71)

RNA H19 is a non-coding RNA, member of LncRNAs, is a major gene in cancer that is expressed in all types of cancer including HCC.(72) It protect oxidative stress in cancer cells by NFk activation. It also shows CCs resistance via MRK/ERK pathway. Oxidative stress plays a role in activation of MAPK pathway and ERK1/2 through ROS accumulation. H19 downregulation induce oxidative stress and correspondingly its response to anticancer drugs in HCC, therefore its inhibition will reduce oxidative stress and CCs resistance by blocking MRK/ERK pathway. Targeting H19 may provide a possible therapeutic target(73). ncRNA-hPVT1 is another long-coded RNA which was found to be upregulated in HCC patients. It favors HCC cancer cycle and its multiplication as well as enabling it to acquire CSCs properties by stabilizing NOP2 protein. Regulation of the lncRNA-hPVT1/NOP2 pathway effective for HCC treatment.(74)

3.1.3 Lung cancer

Accumulation of 8-oxo-7,8-dihydro-2'-deoxyguanosine 5'-triphosphate (8-oxo-dGTP) has been found in cancer cells which makes it to express an elevated level of MTH1 in nucleotide pool to remove this oxidized form of dGTP, an 8-oxo-dGTP.(75). A study was performed where short interfering RNA in a knockdown method is used to regulate the induced toxicity of MTH1 on lung cancer (LuC) cell lines of both p53 mutated and wild type. The experiment suggested that the knockdown of MTH1 resulted in an elevated level of destruction caused to DNA and it signaling pathways in the cancer cell lines in contrast to normal MRC-5 lung fibroblasts used. It also resulted in decreased proliferation but was unable to promote apoptosis or enhance the efficiency of chemotherapeutic drugs. MTH1 has non-small LuC cells that are not dependent on p53 and surprisingly the basis of this may not be ROS associated oxidative stress. Thus to treat the nonsmall LuC the therapeutic targeting of MTH1 may not be an effective approach as it initiates DNA damage without toxicity which could favor cancer heterogeneity and evolution.(76)

An elevated level of cholesterol in mitochondria may results in carcinogenesis and resistance to chemotherapy, reduce cell stress and the release of cytochrome c from mitochondria, increased sensitivity to high amplitude swelling and damage to energetically potent mitochondrial proton leak.

It also decreases mitochondrial membrane permeability (MOMP). Mitochondrial cholesterol will prevent apoptosis with its building up will modify mouse liver cells, neurons and white blood cells to tumor necrosis TNF family Fas ligand. which is followed by mitochondrial MGSH cannot be synthesized in mitochondria and has to be transported from cytosol by special carrier molecules like Dicarboxylate (DIC) and 2-oxoglutarate (OGC). This transport of OGC is dependent on level of cholesterol in mitochondria. A study was performed to identify role of these carriers in HCC with its relation to cholesterol and membrane fluidity by using purified mitochondrial fractions from HCC cells. The human and rat mitochondria of HCC both demonstrated an elevated level of cholesterol but with an unexpected mGSH levels from HCC cells which were identical to those found in mitochondria from non-tumor tissues levels from HCC cells were similar to mitochondria from nontumor .The p53 was not expressed hence demonstrated that elevated mt-cholesterol and maintenance of mGSH is not dependent on p53. HCC cells maintain physiological mGSH despite the sensitivity of mGSH transport to cholesterol-mediated changes in membrane fluidity. There has long been a crosstalk between cancer and its dependence mitochondrial metabolism for survival growth and hemostasis.(77) Another study disclosed that OGC Favors growth of cancer cells by maintaining mGSH level and through regulation of redox hemostasis. Its suppression enhanced lipid peroxidation of cardiolipin which upturned the cholesterol blocking on liposomes. Its knockdown was thus effective in decreasing CSCs properies of LC. In HCC its used as an adaptive mechanism to overexpress OGC to supply sufficient mGSH level for mt-cholestrol therefore suhhesting OGC as a novel taget for HCC treatment.(78)

Oenothein B is an isolated polyphenol with wide range of biological activities (79). It acts as anticancer agent against lung cancer A549 cell. It decreased the cell proliferation, induced apoptosis and arrested the cell cycle at G1 phase. It also elevated the production of ROS and promoted the expression of some of the protein associated with apoptosis and that includes cleavage caspase-3, PARP, cytochrome c level in the cytosol and Bax. The use of ROS blockers and that of PI3K agonist displayed a great amount of protection against apoptosus by Oenothein B. The inhbitors also discontinued by Oenothein B he activation of caspase 3 7 and 9 levels of p-Akt and p-Akt, p-NF-κB inhibition by Oenothein B could be counterbalanced by treatment with ROS inhibitor. Thus the Oenothein B stop the growth of cancer cells by ROS-mediated PI3K/Akt/NF-κB signaling pathway.(80)

CSCs have high expression of ATP-binding cassette transporter proteins, especially ABCG2 through transporter ABCG2. This make these cells highly resistance to chemotherapy. The drugs mostly target CSCs by inhibiting the associated pathways of cells or disrupting the microenvironment surrounding these cells or inhibiting the specific metabolic changes of these cells. Targeting glycolysis pathway, glycolytic enzyme and mitochondria has also been proved to have helpful in removing CSCs. ROS also effect CSCs. The synergic treatment option would be to concurently increase ROS generation as well as blocking glycolysis. Auranofin (AF) is a gold complex drug that is in clinical trial significantly decrease SP cells by elevating ROS production and blocking the glycolytic enzyme hexokinase. Its combination with conventional chemotherapeutic drug is found to be more effective. This drug was effective against lung cancer lines A549, NCI-H460, SkMES-1, Hcc827. AF decreased cell viability and cell markers in a dose dependent manner.(81)

3.1.4 Pancreatic cancer

PDAC involves an increased ROS level accompanied with oxidative stress which results in reduction of antioxidant capacity in patients. This capacity can be restored by the use of antioxidant supplementation. These supplements reduce pancreatic stellate cell activation that is induced by hyperglycemia. One such an antioxidant agent is Coenzyme Q10 (CoQ10) which results in suppression of activation of PSCs mediated by PI3K/AKT/mTOR signaling pathway. CoQ10 is correlated with the downregulation of autophagy via the PI3K-AKT-mTOR signaling pathway. CoQ10 can likely be a remedy for clinical therapy of pancreatic fibrosis (82). Inhibiting AKT3 pathway through Nrf2 PDAC exhibit activation of KRAS mutation and inactivation of tumor suppressors TP53, P16/INK4A, SMAD4. In oxidative stress Nrf2 upregulates ARE associated genes, promotes PIN and initiates PDAC. Cysteine thiol group of amino acid can act as redox switches and the changes in redox potential can interfere with the catalytic activity and protein conformation. An increased level of Nrf2 is seen in PDAC which can lower ROS and these redox switches may downstream Nrf2 effectors to support PDAC progression. A number of cellular events are disturbed due to oxidative stress and that includes mRNA translation and processing. In cancer cells mutations that deregulate mRNA translation are most common. A study was performed where Nrf2 was used to directly stimulate mRNA translation. It also maintained the cysteine residue in its reduced state in proteins that participate in translation of this mRNA. Furthermore, it also promoted the EGFR autocrine cell signaling through Akt/PKB signaling pathway in KRAS dependent cells to fuel cap dependent translation initiation which promotes protein synthesis in PDAC. Intracellular synthesis of glutathione and inhibiting the Akt pathway inhibit PDAC progression thus making it a good target for potential therapeutic applications.(83) PC is usually treated by fluorouracil (FU)- and gemcitabine (GEM) chemotherapeutic agents which is found to be effective in the early stages. However, the unpredictably for the reoccurrence and the likely re-progression of the disease reduces the chances of patient's survival from this type of cancer. CSCs are thought to be the major cause of its reoccurrence as they have very high resistance. The mechanism involved for chemoresistance against 5-FU and GEM between pancreatic CSCs and their non-stem counterparts, is due to JNK pathway which is critically involved in pancreatic CSCs' resistance to these chemotherapeutic agents through suppression of the ROS. Targeting this JNK - "ROS defense" axis in combination with current chemotherapeutic regimens may be a rational approach to overcome the therapy resistance of PC.(84)

Light to target cancer cells which uses photoactivatable compounds (porphyrins and their derivatives) has also been used to treat PC, alone as well as synergically with GEM. ProtoporphyrinIX (PpIX) has been used in photodynamic therapy which induces cell death in different cancer lines. It stabilizes and activates TAp73 and induces TAp73-dependent apoptosis in cancer cells lacking TP 53. TrxR1 has a role in maintaining redox homeostasis in cells and also contributes in progression of tumor. The overexpression of this protein makes it a favorable target for therapeutic applications. PpIX and benzoporphyrin derivative induce ROS and genes HMO X-1 and NQ O1 that are produced in response to ARE. The in vitro inhibition of this selonoprotein by PpIX and BPD in PC cells is due to mutant p53, TP53 mutation which is via are activation of TAp73 tumor suppressor. Targeting both TAp73 and TrxR by small molecules may overcome resistance developed in PC. The simultaneous activation of TAp73 and inhibition of TrxR will significantly increase the stress burden in already stressed cancer cells when compared with separate approaches, is an effective approach in killing cancer cells selectively without affecting normal cell.(85) Tumor

necrosis factor-related apoptosis-inducing ligand. (TRAIL), a member of TNF family is a protein functioning as a ligand that acts as anticancer agent by inducing apoptosis. A study determined the effect of ROS and caspases in TRAIL-induced apoptosis and necroptosis of PC cell lines MiaPaCa-2 and BxPC-3 with cells characterized by Kras and P53 mutations. Treatment of these cell lines with TRIAL resulted in ROS inhibition with increased population of annexin V-/propidiumiodide (PI)+ early necrotic cells suggesting the role of ROS and the involvement of regulatory role of caspase-2 and caspase 9.(86) A study was performed to determine the anti-cancer mechanism of lycopene by determining the expression levels of inhibitors of apoptosis in human PC cells, PANC-1. These PC cell lines were exposed to a varying concentration of lycopene or caspase-3 inhibitor Z-VAD_FMK. MTT assay was used to study the cell while the real-time PCR was used for determination of expressions of inhibitor of apoptosis (survivin) and cellular inhibitors of apoptosis (cIAP-1 and cIAP-2). The result suggested a decreased cell viability of PC treated with lycopene while caspase inhibitor Z-VAD FMK suppressed lycopene-induced cell death. Furthermore, lycopene decreased mRNA expression of survivin, cIAP1 and cIAP2 in PC cells. lycopene induces the apoptosis of PC cells by suppressing the expression of survivin, cIAP1 and cIAP2 and therefore may act as therapeutic agent against PC.(87) Human antigen R (HuR) regulates is also known to regulate the expression of IAP1 and IAP2 in PDAC by binding to these inhibitors of apoptotic proteins.(88)

Mammalian STE20-like kinase 1 (MST1) are closest analogues of pathways and has a role in suppression of PC with a resulted decrease in its progression. MST1 suppressed PDAC and induced pyroptosis via elevating ROS species making it a targetable biomarker for therapeutic target in PDAC.(89)

Blocking Transferrin receptor (TfR1) with monoclonal antibodies.Transferrin receptor (TfR1) regulates iron uptake and iron hemostasis, over expression is observed on the surface of cancer cells including the PC which contribute to oxidative phosphorylation and plays a role in mitochondrial respiration, ROS production and thus growth and survival of PC. Blocking this receptor with monoclonal antibodies has been successful against cancer cells making it a good target for therapeutic application(90)

Even in an oxygen rich environment cancer cells have the ability to maintain high glycolytic activity and an increased lactate production (Warburg effect). Pyruvate kinase M2 isoform (PKM2) is selectively expressed in cancer cells which plays a role in Warburg effect. An increased level of this isoform has also been seen in PCCs. A small interfering and short hairpin RNAs were introduced in PCCs for the purpose of inhibiting PKM2 and the results were assayed using microarray analysis and gene expression profiles in the cells. The knockdown of PKM2 mediated RNAi inhibits the multiplication, migration growth and progression of the PDAC cell-lines. The knockdown also resulted in decreased level of activities performed by glycolysis as well as low level as pyruvate and polyamine. But it resulted in increased production of ROS. Cancer cells and proliferative tissue reprogram its glucose metabolism and consume larger amount of glucose and using glycolysis produces lactate even in oxygen rich environment. The phenomenon known as Warburg effect. PKM2 regulates final step of glycolysis by converting phosphoenolpyruvate and ADP into pyruvate and ATP. PKL of the four isoforms of PKM2 are expressed in different types of cancer cells including PCCs. It favors the tumor formation process by controlling the Warburg effect. In an Immuno deficient mice the downregulation of PKM2 resulted in the increased consumption of oxygen and decreases glucose uptake and lactate production. When the activity of this enzyme is

regulated it increased the cell multiplication and tumorigenesis. The hypoxiainducible factor (hIF)-1 plays a role in hemostasis and increase the nutrient and oxygen concentration in depleated cells by vascularization. The PKM2 interacts with this factor to maintain the glucose hemostasis in tumor cells. It also regulates the cell cycle progression by making use cyclin D1, a G1 phase protein and c-Myc expression by phosphorylating histone h3 at threonine 11 (h3-T11). This would be result in separation of chromosome, G1-s phase transition, progression through cell cycle stages and formation of tumor. It is upregulated in PDAC tissue and its knockdown decreases tumor growth by changing the gene expression that drive the cell-cycle G1-s phase transition and the production of intercellular metabolites, particularly spermine, which induces transcription. PKM2 hence direct the cell cycle to divide the cells controllably in PDAC and can make a good pharmaceutical target.(91) ROS regulation is a major extra-ribosomal function in PCCs and could be used as an indicator for the its tumorigenesis. ROS hemostasis can be regulated by mitochondrial ribosomal protein RPL10 by entering into mitochondria. It is known to modulate the activity of complex I of mitochondria and also playing a role in ATP formation. RPL10 could affect the expression of redox related proteins to regulate ROS balance and cellular processes in PCCs. Mitochondria has the ability to maintain this hemostasis and amount of ROS by glutathione (GSH) and peroxiredoxins(92).

Berberine (BBR) is a naturally occurring isoquinoline quaternary alkaloid compound that is found in variety of different fruits. It is effective against various diseases including cancer. It influences the expression of various processes such as apoptosis, metastasis and various genes BCL2, BCLXL, PARP etc. BBR suppress the growth of PCCs by suppression of cell cycle progression, induction of ROS and induction of apoptosis. Modified BBR compounds show enhanced anticancer activities which is possibly due to DNA damage, induction of ROS species, induction of apoptosis and autopathy.(93) The two biologically active components of plant are cannabidiol (CBD) and tetrahydrocannabinol (THC). It reduces tumor growth.(94) Gambogic acid induces autophagy process which improved PCCs survival with the expression of LC3-II and Beclin-1 proteins as demonstrated by xenograft model of PCCs. It decreased MMP, increased ROS production which helped activation of autophagy. Chloroquine further facilitate this process and inhibits autophagy showing cellular protective effect. Gambogic acid induces autophagy mediated cytoprotection in PCCs. Upon inhibition of autophagy the Cellular cytotoxicity induced by gambogic acid is increased via building up of ROS in PCCs. Therefore the use of gambogic aid and chloroquine together can acts as an effective treatment for Pancreatic cancer (95). Several phytochemicals may induce p53 activation which may produce ROS species and can be used for cancer treatment(96) Presence of secondary metabolite make natural plants effective anticancer agents with less to no toxicity that is usually associated with other treatments of cancer therapy. Given below is a table representing different plant extracts that can be effective against PC cell lines

Table 1 phytochemicals as pancreatic drug

Compound	Cell line	Mechanism	Reference

Sugiol	Mia-PaCa2	ROS-mediated alterations in MMP favoring apoptosis, cell cycle arrest in G2/M phase, upregulated the expression of Bax, downregulation of Bcl-2	(97)
Inula helenium L	CFPAC-1	The ethyl extract of plant inhibit profileration of PC cells ,induces mitochondrial mediated apoptosis and inhibit cell migration through STAT3/AKT pathway.	(98)
dietary/herbal spice curcumin (Cur) and COX inhibitors	N/A	COX-independent mechanism was followed where combination of Cur+TA caused increase in apoptotic markers, ROS levels and augmented NF-kB translocation to nucleus. TA caused cell cycle arrest in G0/G1 and the combination treatment showed mostly DNA synthesis phase arrest	(99)
Curcumin derived CUR-loaded magnetic nanoparticle (MNP- CUR)	HPAF-II and Panc-1	suppression of proliferating cell nuclear antigen (PCNA), B-cell lymphoma-extra large (Bcl-xL), induced myeloid leukemia cell differentiation protein (Mcl-1), cell surface–associated Mucin 1 (MUC1), collagen I, and enhanced membrane b-catenin expression.	(100)
Bark extract of angiosperm Pterospermum acerifolium (L.)	PANC-1, A549	cell migration and invasion rate of both the cancer cells were significantly reduced, early apoptotic by arresting the cell at sub-G1 phase after treatment with extract, depolarized the MMP and induced ROS generation	.(101)
Nimbolide isolated from leaves and flowers of Neem	HPAC, MIAPaCa-2, and PANC-1	nimbolide-induced excessive ROS generation lead to mitochondrial- mediated apoptotic cell death of PC with decreased growth, proliferation and metastasis.	(102)

Cotylenin A (CN-A) isolated from patients with acute myeloid leukemia	MIAPaCa-2, PANC-1	CN-A and PEITC, ROS inducer synergistically inhibited the proliferation of PC cell lines and resistance against gemcitabine- resistant. Cell death is due to the induction of ferroptosis	(103)
Piperlongumine found in plant species Piper longum	Panc1 and L3.6pL, A549, 786-O, SKBR3	downregulated expression of Sp1, Sp3, Sp4 and pro-oncogenic Sp- regulated genes cyclin D1, survivin, cMyc, epidermal growth factor receptor (EGFR) and hepatocyte growth factor receptor (cMet), piperlongumine-induced ROS decreased expression of cMyc via an epigenetic pathway and this resulted in downregulation of cMyc-regulated microRNAs (miRs)-27a, miR-20a and miR-17 and induction of the transcriptional repressors ZBTB10 and ZBTB4. These repressors target GC-rich Sp binding sites to decrease transactivation.	.(104)
endophytic fungus strain MRCJ-326, isolated from Allium schoenoprasum	MIA PaCa-2	dicatenarin and skyrin isolated from fungus induce reactive oxygen species-mediated mitochondrial permeability transition and resulted in an increased inductionofcaspase- 3apoptoticproteinsinhuman pancreatic cancer (MIA PaCa-2) cells. Dicatenarin showed a more pronounced cytotoxic/proapopotic effect than skyrin due to the presence of an additional phenolic hydroxyl group at C-4, which increases oxidative reactive oxygen species generation.	(105)
Resveratrol and capsaicin	N/A	Used in combination with radiotherapy increases the formation of ROS and radiosensitivity of PCCs. It strongly inhibit DNA double stranded break repair induced by radiotherapy.	(106)

3.1.5 Ovarian cancer

Tumor is an Oxidative Stress Factor in Ovarian Cancer Patients. (107) Ovarian cancer has a low survival rate of less than 20%. A study showed an increase in the value of ROS emphasizing it as an active oxidative process in patient with ovarian cancer. Lipid peroxidation is significantly higher in patients with ovarian cancer suggesting that the tumor is a generator of oxidative stress. (108) The drug used for the first line treatment is the widely known Gemcitabin which when enters the cells is phosphorylated by deoxycytidine kinase (dCK) into active 2',2'-difluorodeoxycytidine triphosphate (dFdCTP) metabolite. However more than 90% of this drug is converted into inactive form before it can even inhibit DNA replication and induce apoptosis of cancer cells. Interference of CDA expression in cancer cells could decrease GEM inactivation, leading to increased drug uptake at the tumor site. Artemisinin an active compound of herb, Artemisiae annuae has potential anticancer activity. Artemisiae annuae and its analogue Dihydroartemisinin (DHA) has endoperoxide bridge that can be activated by heme or ferrous iron to produce the cytotoxic reactive oxygen species. The analogue thus can undergo programmed cell death by the pathway of apoptosis associated with elevated ROS generation which subsequently causes oxidative stress and the damage that results due to it. The alteration of redox hemostasis and the increased oxidative stress is thought to be related with increased expression of heme oxygenase-1 (HO 1) which could further suppress cytidine deaminase (CDA) expression in cancer cells. The use of combination of DHA and the chemotherapy drug (gematacibine) has more anticancer potential. more than 90% GEM is catalyzed into an inactive metabolite 2'-deoxy-2',2'difluorouridine by stromal and cellular cytidine deaminase (CDA) The endoperoxide bridge .The study made a similar hypothesis that DHA could induce excess ROS production, elevated oxidative stress, greater expression of HO-1, suppression of CDA expression with low expression of CDA the reduction in GEM inactivation is observed. The ovarian cancer cell line A2780 was used insuch study with the result indicated the synergic treatment of DHA and GEM to be fruitful as anticancer agent showing low toxicity than which is normally experienced in GEM with the ability to effectively eliminate the ovarian tumor at day 14.(109)

miRNAs have been reported to be differentially expressed in CSCs compared to their corresponding bulk cancer cells. identification of dysregulated miRNAs in ovarian CSCs will be crucial for elucidating the mechanism underlying the maintenance of CSC properties, and then benefit to develop novel therapeutic methods to target and eliminate CSCs. miR-328-3p (termed miR-328) is highly expressed in ovarian CSCs, and plays a critical role in the maintenance of CSC properties as well as ovarian xenograft metastasis by directly downregulating DNA damage binding protein 2 (DDB2). high expression of miR-328 is due to a reduced activity of ERK signaling in ovarian CSCs caused by a low intracellular level of reactive oxygen species (ROS) in these cells. Cancer stem cells (CSC) play a central role in cancer metastasis and development of drug resistance. MicroRNAs (miRNA) are important in regulating CSC properties and are considered potential therapeutic targets. Here we report that miR-328-3p (miR-328) is significantly upregulated in ovarian CSC. High expression of miR-328 maintained CSC properties by directly targeting DNA damage binding protein 2 (DDB2), which has been shown previously to inhibit ovarian CSC. Reduced activity of ERK signaling in ovarian CSC, mainly due to a low level of reactive oxygen species (ROS), contributed to the enhanced expression of miR-328 and maintenance of CSC. Inhibition of miR-328 in mouse orthotopic ovarian xenografts impeded tumor growth and prevented tumor metastasis. In summary, our findings provide a novel mechanism underlying maintenance of the CSC

population in ovarian cancer and suggest that targeted inhibition of miR-328 could be exploited for the eradication of CSC and aversion of tumor metastasis in ovarian cancer. In summary, we demonstrated that the ROS-ERK-miR-328-DDB2 axis plays a critical role in driving EOC progression by facilitating the maintenance of CSCs in tumors. Thus, inhibition of miR-328, or interruption of the ROS-ERK-miR-328-DDB2 axis can be exploited for the development of efficient strategies for eliminating CSCs to prevent ovarian tumor metastasis and recurrence, eventually leading to an improvement of the survival of EOC patients. (110)

celastrol inhibits the growth of cell by arresting the cell at its G2 and M phase of cell cycle and induces cell death with the elevated ROS with building up in ovarian cancer cells. Treating the cancer cells prior with ROS scavenger N-acetyl-cysteine inhibit the apoptosis induced by celastrol. It also inhibits the growth of ovarian cancer xenografts in nude mice. Thus celastrol is an effective anticancer agent for ovarian cancer.(111)

paclitaxel (PTX), a natural product present in the Pacific yew, Taxus brevifolia is used as chemotherapeutic agent. The problem with the use of such drugs is the development of resistance because of prolong use and the reduction of the dose of these drugs to avoid toxic effect which intron reduces its effectiveness. Gallic acid is a phenolic compound with potential antioxidant activity in biological systems and has the ability to induce apoptosis. The GA not only prevent oxidative stress but also increase the ROS generation and with the ROS being associated with a number of cellular processes that includes cell multiplication, cell death and the resistance shown by chemotherapy drugs. These ROS induced processes are associated with upregulation or downregulation of several proteins that includes protein kinase activities, such as PI3K/Akt, MEK/ERK and p38-MAPK. A study analyzed the ability of GA to enhance the anti-proliferative action of PTX in ovarian carcinoma cells. Two cell models were used, namely the A2780 cell line and a doxorubicin-resistant variant A2780AD, which overexpresses P-glycoprotein. The result demonstrated that the A2780AD cells are less sensitive to PTX than A2780 cells, and that the cytostatic action of PTX is increased in both cell models via co-treatment with GA, which potentiates the PTX-induced G2/M phase arrest. Using the drug-resistant cell line, it was also observed that the proliferation inhibition and G2/M phase arrest are mediated by GA-provoked ROS overproduction, and by ROS-mediated inhibition of PTX-provoked ERK activation. (112)

The production of ROS is reported to be involved with the epithelial ovarian cancer type CAOV-3, the most common type of ovarian cancer. A group of sciientists synthesized a compound MS-5 which is a derivative of naphthalene for the purpose of its anticancer agent againt the ovarian cancer. The synthesized compound decreased the production of intracellular ROS with the ability to induce alteration in the vell morphology and its viability. The inhibition of cancer cells was found to be in a dose and time dependent manner with the treatment suggested an elevated cell death by apoptosis in contrast to control cells with MS-5 induces the regulation of Bcl-2 and Bax balance with induced activation of caspase-9, caspase-7 and caspase-3, and cleavage of PARPThe iintrinsic pathway was thus found to be involved in the process and for the purpose of h study the expression level of BCl-2 was examined and it was found that the its level was downregulated along with the survvin protein when treated with MS-5. The balance of the Bax and BCl-2 was associated wuh the mitochondrial release of cytochrome c into the cytosol. MS-5 also induces G1 cell cycle arrest in CAOV-3 cells with the compound causing the profound building up of CAOV-3 cells in G1 phase. Western blotting analysis showed that there is a decrease in the levels of CDK2, cyclin

D1, whereas the level of protein p27 increased by the treatment of MS-5. Its effect on ROS was observed which indicated that the the accumulation of ROS can induce cell death. In order to determine the production of ROS by treating it with MS-5, an oxidation-sensitivedye H2DCFDA was used which indicated the decreased prodictioon of ROS upon treatment with MS-5. Thus MS-5, a derivative of naphthalene, induced apoptosis and G1 phase arrest of CAOV-3 cells by interfering with the ROS-regulated signal transduction, and elucidation of molecular mechanism may lead to a new target for the treatment of ovarian cancer. (113)

There are some compounds such as noscapine which induce apoptosis In ovatian cancer showing its dependence on Bitter taste receptors (Tas2Rs) and not on ROS . (114)

Amoung various drug types used as an option for treatment of ovarian cancer, platinium drugs is one of them. However the cancer cells aquire resitance to it and the resistance may be due to increase of DNA damage response. dual oxidase maturation factor 1 (DUOXA1) is overexpressed in platinum resistant ovarian cancer cells, resulting in increased generation of ROS. This elevated ROS assists the activation of ATR-Chk1 pathway, leading to resistance to cisplatin in ovarian cancer cells. Further two Chk1 inhibitors (PF-477736 and AZD7762) has also been identified that resensitize resistant cells to cisplatin. Blocking this novel pathway by inhibiting ROS, DUOXA1, ATR or Chk1 effectively overcomes cisplatin resistance. The clinical trial also confirmed that the activation of ATR and DOUXA1 in ovarian cancer patients, and elevated DOUXA1 or ATR-Chk1 pathway correlates with poor prognosis. Thus this study provided a new mechanism regulating cisplatin resistance, as well as a multiple combinational strategies to overcome platinum-resistance in ovarian cancer(115)

A study was performed to evaluate the anticancer potential of Sideroxylinisa C-methylated flavone isolated from Callistemonlanceolatus. The sideroxylin decreased cell proliferation and increased apoptosis, causing DNA fragmentation, depolarization of the mitochondrial membrane, the generation of reactive oxygen species, and an increase of lipid peroxidation in ovarian cancer cells (ES2 and OV90 cells). It also activates the phosphorylation of ERK1/2, JNK, P38, and MAPK proteins in ES2 and OV90 cells. Thus the sideroxylin combat the proliferation of ovarian cancer cells through the induction of mitochondrial dysfunction and the activation of PI3K and MAPK signal transduction.(116)

Chinese medicinal herb is nowadays widely used for cancer treatment and it is found to be effective in controlling the progression of cancer. One such drug is Withaferin A is originated from herbal plant. It shows anticancer properties by activation of Akt. It induces ROS, mitochondrial membrane and phosphorylation of histone H2A and kill oral cancer cells. It inhibits STAT3 in colorectal cancer. ROS effect mitochondrial membrane potential and trigger cell apoptosis by JNK pathway in cancer. In the study performed to determine the effect of Wuthaferin A on colorectal cancer and it was found that the antitumour effect followed the loss of membrane potential, elevated ROS, capase activation, regulation of BCl2 family members and cell cycle arrest.(117)

3.1.6 Cervical cancer

The persistent activation of transcription factor Nrf2 has long known to associated with cancer types including cervical cancer. Its knockdown by small hairpin RNA shRNA results in inhibition of growth tumor of CCs with increasing its sensitivity to chemotherapy drug.(118) CCs is also associated with oxidative stress, disturbance of redox hemostasis results in over

production of ROS which results in damage to biological entities.(119) The oxidative stress is associated with growth and initiation of female related cancer that includes breast, ovarian and cervical cancer. The body of evidence indicates that ROS can induce, promote and modulate carcinogenesis Anti-oxidation system as enzymatic and non-enzymatic antioxidants defends against OS, including oxidation and reduction of molecules that lead to free radical production(120) OS is directly associated with several pathological conditions including tumors associated with human papillomavirus (HPV) infection resistant infection with high-risk HPV types (HR-HPV) is the main etiological cause for the development of several epithelial tumors at different anatomic locations. The most strongly HPV-associated malignancy is cervical carcinoma, where almost all tumors are positive for HR-HPV DNA(121) EF24 acts as anticancer agent against CCC and is due to oxidative stress induced by ROS. Curcumin another natural compound has analog EF24 which inhibit cell viability (percentage of cell that are living) and programmed cell death with an increase of ROS production. It led to depletion of total intracellular GSH levels, induced mitochondrial depolarization, and abrogated STAT3 phosphorylation. (122)

3.1.7 Thyroid cancer

The activation of the RET proto-oncogene contributes to the development of human cancers including Medullary thyroid cancer (MTC). Cellular transformation through activation of signaling pathway is contributed by the expression of RET protein complex. The current drugs used for the treatment of MTC are tyrosine kinase inhibitors (TKIs) cabozantinib and vandetanib. These inhibitors increase MMP potential causes bioenergetics stress and their combination with mitochondrial-targeted agents suppresses MTC tumor growth in mice. Targeting mitochondrial HSPA9 (GRP75/Mortalin) suppress human MTC cells in culture and in mouse xenograft. Targeting protein homeostasis pathways could be exploited for the treatment of tumors with high protein synthesis rate. combination of an ATF4 inducer and a TKI causes excessive cellular oxidative stress resulting in the activation of apoptosis. combinations of TKIs and eevarestatin, a conventional drug used for treatment of thyroid cancer induced apoptosis in MTC cells in vitro through an increase in ROS and upregulation of ATF4 and ATF4 target genes. MTC originates from the C cells of the thyroid gland, which secrete calcitonin, these cells are highly reliant on their UPR and ERAD pathways as a result of their high protein synthesis burden. Thus, increasing ATF4 expression in MTC tumors may constitute a therapeutic strategy for inhibiting tumor growth through increasing the expression of tumor suppressor genes. Increased ER stress is common in most types of human tumors, inducing ER stress and oxidative stress sufficiently to induce death of cancer cells but not normal cells could be a useful new approach to cancer treatment.(123) Eleavated thyroid harmones are associated with oxidative stress as these harmones have a role in respiration, ATP formation and mitochondria functioning. It plays a role in the onset of Various neurodegenerative diseases(124)

3.2 Angiotensin II

Angiotensin II increases ROS production in podocyte of Bowman's capsule. H_2O_2 induces rapid mobilization of Ca2-permeable TRPC6 channels in cultured podocytes signaling through the .over-expressed type 1 receptor of Angiotensin II in podocyte cells can lead to activation of TRPC6 and TRPC5 channels. Studies in primary mouse podocytes indicated that AII can evoke an increase in cationic currents that is not seen when the dissociated cultures are prepared from constitutive TRPC6 knockout mice. AII causes a concentration-dependent increase in cationic currents through channels containing TRPC6 subunits. AII activation of cationic currents in primary podocytes was blocked by the AT1R inhibitor losartan, and also by inhibition of phospholipase C (PLC). Crucially, this cascade also required generation of ROS, as the response was blocked by two different ROS quenching agents, and a general inhibitor of NADPH oxidase (NOX) enzymes. These data indicate that generation of ROS is an essential part of the normal transduction cascade used by AII in podocytes, and that TRPC6 comprises the primary channels involved in the cascade that leads to increased cation influx in these cells.

Canonical transient receptor potential-6 (TRPC6) channels stimulate Ca2b influx in podocytes, and have been implicated in glomerular disease. We observed that AII increased cationic currents in rat podocytes in an isolated glomerulus preparation in which podocytes are still attached to the underlying capillary. This effect was completely blocked by SKF-96365, by micromolar La3b, and by siRNAknockdownofTRPC6, indicating that TRPC6 is the primary source of Ca2 pinflux mobilized by en dogenouslyexpressedangiotensin II receptors in these cells. These responses were also blocked phospholipase C D-609, the AT1R antagonist losartan, the inhibitor bv and byinhibitionofGproteinsignaling.The protein kinase inhibitorchelerythrinehadnoeffect.Importantly, pretreatingpodocytes with the ROS quencher manganese (III) tetrakis (4-benzoic acid) porphyrin chloride (MnTBAP) eliminated AII activation of TRPC6. Significant reductions of AII effects on podocyte TRPC6 were also observed after pretreatment with NADPH oxidase inhibitors apocynin or diphenylene iodonium (DPI). These data suggest that ROS production permits activation of TRPC6 channels by G protein and PLCdependent cascades initiated by AII acting on AT1Rs in podocytes. This overload—converge on common pathways relevant to diseas(125).

Genomic analysis confirmed that the Insulin resistance is associated with ROS species, the increase ROS level trigger insulin resistance.(126) Angiotensin II–Induced Reactive Oxygen Species and the Kidney

3.3 Cardiovascular diseases

There are various factors that increase the risk of heart diseases and that includes hypertension(127), obesity, stress(128, 129), Water pipe (hookah) smoking(130) etc. Nowadays oxidative stress mediated cardiovascular diseases is also regarded as one of the primary or secondary cause(131). As a result of the aforementioned diseases the alteration of the expression of enzymes that are responsible for production of reactive species is changed and this results in increased formation of ROS. The increased production in turns favors these disorders directly and cardiovascular disease indirectly. The associated risks, oxidative stress and ROS production also initiates several pathways(132) like apoptosis of endothelial cells or migration of smooth muscle cells, lipid peroxidation and several more which collectively contribute to the progression and likely occurrence of the cardiovascular diseases.(133) The controlled production of ROS has a role in cardio protection while its elevation supports cardiovascular driven diseases. (134) Mitochondria plays an important role in cardio protection by opening the ATP driven potassium channels which leads to the elevation of ROS results in activation of mitoKATP-associated PKC_{\varepsilon}, which phosphorylates mitoKATP and leaves it in a persistent open state. The signaling of

this ROS is found to be downstreamed by OH radical of H2O2 which is is probably a product of phospholipid oxidation.(135)

There are a number of diseases that are characterized as cardiovascular and that includes coronary artery disease (CAD), stroke, hypertension, heart failure, rheumatic aetiologies, congenital heart disease and peripheral vascular disease, coronary heart disease, and myocardial infarction. Atherosclerosis a characteristic and dominant cause of cardiovascular disease with a relationship with ROS production as it effects on molecule's underlying endothelium that can initiate apoptosis, necrosis and therefore thrombosis of atherosclerotic plaques makes oxidative stress a crucial hallmark of CVD and is defined as its early causative factor(132) The increase in ROS production derived from dysfunctional endothelial and vascular smooth muscle cells contributes to a series of vascular restructures (e.g., the proliferation of vascular smooth cells, thickening of the intima, remodeling of the artery, pulmonary hypertension and changing in fluid dynamics), leading to blood vessel stenosis and atherosclerosis(136)

3.4 Neurodegenerative diseases

Neural cells has been attacked by oxidative stress leading to neurodegenerative disorders. Elevated ROS production results in nuero disorders such as Alzhimers diseases, dimensia, parkinsons and aging related diseases. Neuronal damage by the use of antioxidant agents in the form of natural plant based herbs and dietry components has attracted attention of scientists. Mitochondrial (Mt) dysfunctions and excitotoxicity followed by apoptosis have been reported as pathological cause for aging and neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), Multiple Sclerosis (MS) and amyolotrophic lateral sclerosis (ALS).(137) An important form of antioxidant defense is the storage and transport of iron and copper ions in forms that will not catalyze formation of reactive radicals. Tissue injury, e.g., by ischemia or trauma, can cause increased metal ion availability and accelerate free radical reactions. This may be especially important in the brain because areas of this organ are rich in iron and CSF cannot bind released iron ions. Oxidative stress on nervous tissue can produce damage by several interacting mechanisms, including in- creases in intracellular free Ca2+ and, possibly, release of excitatory amino acids. Recent suggestions that free radical reactions are involved in the neurotoxicity of aluminum and in damage to the substantia nigra in patients with Par- kinson's disease are reviewed. Finally, the nature of antioxi- dants is discussed, it being suggested that antioxidant en- zymes and chelators of transition metal ions may be more generally useful protective agents than chain-breaking an- tioxidants. Careful precautions must be used in the design of antioxidants for therapeutic use(138) ROS formation enhances in humans that are sensitive to salt with induced hypertension. This increased ROS is produced by brain which consequently elevates blood pressure by central sympathoexcitation. It has been suggested that ROS production in the brain and central sympathoexcitation may share a common pathway that increases BP in both salt- and obesity-induced hypertension(139) The bcl-2 gene that is associated with oncogenesis hinder apoptotic and necrotic neural cell death. Expression of Bcl-2 in the GT1-7 neural cell line prevented death as a result of glutathione depletion. Intracellular ROS and lipid peroxides rose rapidly in control cells depleted ofglutathione, whereas cells expressing BcI-2 displayed a blunted increase and complete survival. Modulation of the increase in reactive oxygen species influenced the degree of cell death. Yeast mutants null for superoxide dismutase were partially rescued by expression of Bcl-2. Thus, Bcl-2 prevents cell death by decreasing the net cellular generation of reactive oxygen species(140)

3.4.1.1 Alzheimer's disease

It is a form of dementia characterized by progressive loss of cognitive behavior and brain cells which becomes worsens over time. Neuropathalogical changes include lesions such as amyloid plaques and cerebral amyloid angiopathy, neurofibrillary tangles, and glial responses, neuronal and synaptic loss (141). Amyloid beta (AB or Abeta) derived from amyloid precursor protein (APP), formation and its deposition is strongly associated with AD.(142) soluble oligomers of amyloid beta (ABOs) are involved in pathogensis of AD. This oligomer enhances/promotes the processing of pro-interleukin (IL)-1b into mature IL-1b in microglia, which then enhances microglial neurotoxicity. The processing is induced by an increase in activity of caspase-1 and NOD-like receptor family, pyrin domain containing 3 (NLRP3) via mitochondrial reactive oxygen species (ROS) and partially via NADPH oxidase-induced ROS. The caspase-1 inhibitor Z-YVAD-FMK inhibits the processing of IL-1b, and attenuates microglial neurotoxicity. Our results indicate that microglia can be activated by oAb to induce neuroinflammation through processing of IL-1b, a pro-inflammatory cytokine, in AD.(143) Presenilins (PS1andPS2) transmembrane proteins of endoplasmic reticulum (ER) membrane results in along with APP mutation cause most early-onset, autosomal dominant familial cases of the disease (FAD) Together with nicastrin, APH-1, and PEN-2, PS forms a protein complex that is transported to the cell surface and endosomes, where it functions as a gamma-secretase that cleaves several type 1 transmembrane proteins, including APP.

Gene mutations along with several enviornmental risk factors such as neuroinflammation and oxidative stress are also associated with AD Neurogenesis occurs in the adult brain of mammals, particularly in the hippocampus, and is enhanced in the brain of patients with AD. Enhanced neurogenesis in AD may represent an attempt by the central nervous system to compensate for the neuronal loss and repair itself. Reactive oxygen species (ROS) promote cell death and the nondisjunction of chromosomes, leading to aneuploidy. The activity of ROS on newly generated neuronal cells in the adult brain may contribute to the pathogenesis of AD. Antioxidant may be used to reduce the deleterious activity of ROS, particularly on newly generated neuronal cells of the adult brain, potentially delaying the development of AD and promoting the regenerative capacity of the adult brain (144)One of the types of AD that is passed on to the offspring is Familial Alzheimer's disease (FAD). Mutation of APP and that of presenilin genes PS1 and PS2 is responsible for the early onset of the disease.(145) These mutations also alter the Ca+2 release and disturb its normal hemostasis by increasing the gating of membrane glycoprotein complex inositol trisphosphate receptor which is responsible for releasing the Ca+2, the altered gene which resulted from mutation acquire a novel molecular function with dependency not dependent on Secretases, which are enzymes that process APP into nonamyloidogenic and amyloidogenic fragments. Examining the B lymphocytes of patients suffereing from FAD for inositol trisphosphate receptor. Mice suffering from PS1 mutation AD and also carry the mutation gene to the offspring demonstrate that these cells exhibit greater probability of opening Ca+2 channels by increased signaling. The enhanced signaling also increases ROS generation which is an important hallmark in AD pathogenesis.

Exaggerated Ca2+ signaling through InsP3R–PS interaction is a disease specific and robust proximal mechanism in AD that may contribute to the pathology of AD by enhanced generation of reactive oxygen species.(146)

The associated metal complexes of APPb protein of AD also been long known as one of the possible mechanisms involved in the neurodegeneration with its ability for the formation of

plaques and fibrils and generation of the ROS such as H2O2 and free radicals. The Ab peptide is oxidized during formation of ROS. (147)Aggregation of ABeta is the characteristic feature found in AD that is induced by metal binding and therefore are commonly observed in the form of metal containing plaques and insoluble fibrils. CuII complexes of metal-binding domains of Ab (CuAb) exhibit metal-centered oxidative catalysis with ability to undergo oxidation of neurotransmitters and this imbalance of neurotransmitters can be demonstrated near the plague Ab_{1-40} in AD. Thus small fragments of Ab can greatly alter neurotransmission in a systematic manner in the brain of AD patients and play a role in neuropathology of the disease.(148) The use of bifunctional compounds with ability to disassemble metal induced A β aggregates has proved to be effective in AD treatment.(149) An advance age of individual with neurodegeneration has been widely reported to be related to elevated level of ROS. The increased oxidative stress can cause damage to the lymphocytes of AD patients. The same type of alterations are also observed when patients are suffering from mutation of APP or PS1 gene. Cells of patients suffering from AD handle oxidative stress differently(150)

This aggregation of $A\beta$ that produces ROS species are also ROS induced inflammation of AD and its subsequent neurodegeneration. Breast cancer resistance protein (BCRP)/ATP-binding cassette subfamily G member 2 (ABCG2) ABCG2 plays a protective role against oxidative stress by decreasing ROS generation, enhancing antioxidant capacity, regulating heme level, and inhibiting inflammatory response in cell models. ABCG2 inhibits NF-jB activation but has less effect on AP-1 activation induced by ROS. This results in inhibition of interleukin-8 and growthrelated oncogene (GRO) expression induced by ROS via NF-jB pathway. Abcg2 deficiency increased Ab deposition and NF-jB activation in the brains of Abcg2-knockout mice compared with controls. These findings suggest that ABCG2 may relieve oxidative stress and inflammatory response via inhibiting NF-jB signaling pathway in cell models and brain tissues and thus may play a potential protective role in Alzheimer's neuroinflammatory response.(151) Dysfunctipining of ETC or compex 1 of mitochondria will result in decreased ATP production and increased ROS generation. (152) The mitochondrial DNA is also sucepted to more likely to undergo oxidative damage in AD patients(153)

3.4.1.2 Parkinson's Disease

Lipid peroxidation induced by ROS is associated with numerous neurological dysfunctionings including parkinsons disease. polyunsaturated fatty acids are the fist target of ROS species, and this PUFA is present in mitochondrial membrane. The reactive species would cause the mitochondrial membrane to disrupt its functioning along with production of toxic carbonyls such as malondialdehyde. A study on mice revelaed that using D-PUFA are effective against oxidative stress, and inflammation produced by α -syn toxicity. It decreased the isoprostane levels more than that PGF2a and also act against non-enzymatic lipid peroxidation hence making it an effective agent in neurotheraphy.(154) Protein aggregation along with oxidative stress are considered to be the primary cause of PD. Alpha-synuclein (alpha-S) aggregates from its monomer to oligomer form with production of ROS and neuron degeneration. The midbrain of PD patients results in dopaminergic neuron loss with aggregation of alpha-S forming inclusions known as lewy bodies or lewy neurons. This primary aggregation step is enough to cause PD.Some structural form of oligomer damage neurons by which ROS is formed in metal ion dependent manner. Oxidative stress due to elevated ROS production can cause damage to protein, lipid and DNA as confirmed by the posparteum brain of patient suffereing from PD. One report suggested the basal lipid peroxidation increases which eventually damages intracellular

components, induce apoptosis. There are various genes mutations that has been identified in PD that can cause not only PD but only disrupt mitochondrial functioning and oxidative stress ultimately resulting in cellular toxicity. Thus the amyloid protein aggregation, oxidative stress induction and death of neurons death is likely central in the pathogenesis of PD.(155)

There are several mechanisms that produce ROS and that includes mitochondrial dysfunction, domaine metabolism, disturbance of Ca+2 hemostasis, Heavy meatal induced oxidative stress has also been reported in which Iron hemostasis disruption results in oxidative stress in PD, Cupper being involved in cell division plays a role in PD neurodegeneration while cobalt produces ROS species and damage to brain cells(156)

The pathology of the PD is assisted by various drug therapies that utilized the ROS reduction mechanism. Metformin is a commonly used drug for diabetes which recently reported also plays a potential role in treating variety of neurodegeneration diseases. It is regarded as AMPK activator and it does so by accelerating phosphorylation of AMPK. It prevents the death of Dopaminergic neurons in 1-methyl-4-phenly-1,2,3,6-tetrahydropyridine plus probenecid (MPTP/P) Mouse Model of PD, increase antioxidant activity via Autophagy enhancement of AMPK and Mitochondrial ROS Clearance. This thus provide basis for clinical trial of the drug(157).

Function of Synphilin-1, a cytoplasmic protein has been done in PD mice model. A mitochondrial complex 1 inhibitor, 1-methyl-4-phenylpyridinium (MPP+), was used for the study. human neuroblastoma SH-SY5Y cell lines were used that expressed Synphilin-1. overexpression of synphilin-1 increased SH-SY5Y cell viability after MPP+ treatment. It also suppressed apoptotic changes in nuclei, including nuclear condensation and fragmentation, after MPP+ treatment with ability to greatly reduce MPP+-induced cleaved caspase-3 and cleaved poly-ADP-ribose polymerase levels. ROS Formation induced by MPP+ was also to greater extent decreased in cells expressing synphilin-1. It inhibited MPP+-induced cytochrome c release from mitochondria into the cytosol. Thus synphilin-1 may function to protect against dopaminergic cell death by preserving mitochondrial function and inhibiting early steps in the intrinsic apoptotic pathway. synphilin-1 may play neuroprotective roles in PD pathogenesis by inhibiting ROS production and apoptosis (158). Using naturally isolated compounds for treatment of neurogenerative disease has been in practice for decades.(159-162) Salidroside (Sal), a phenylpropanoid glycoside an isolate of Rhodiolarosea L has potent antioxidant properties. Dopamine releasing neurons, dopaminergic neurons are protected by the extract by hindering the ROS and NO. It also proctected the neurons against MPTP/MPP+-induced toxicity and regulated Bcl-2/Bax ratio. Decreasing cytochrome c release from mitochondria, inhibiting caspase-3, 6,9 activation, reducinga-synuclein aggregation. Sal may act as an effective neuroprotective agent through modulation of the ROS-NO mediated by mitochondrial pathway in vitro and in vivo(163) Rasveratol is another natural isolate found in variety of food paroducts and has a role in neuroprotection and can possibly be used for parkinsons and Alzhimers. (164)

3.5 Kidney and oxidative stress

Animal model proved the relationship of oxidative stress on renal damage, and its association with obesity and diabetes.(165)Aquaporin-11 selectively regulate water in and out of a normal kidney. Its deficiency along with disruption of normal oxygen hemostasis would result in kidney injury. The analysis of extracted genes and its pathways determined that the Genes expression of NADPH oxidase 2 (NOX2) complex was increased 14 fold with ROS production. The protein

level of the complex and marker protein for macrophage in the kidney of *Aqp11^{-/-}* mice was also increased in the tissue surrounding the renal medulla known as renal interstitium. This indicated the oxidative stress induced by NOX2 followed by macrophage infiltration take part in changes to the hemostasis of oxygen. .(166) Bioenergy variations of mitochondira oxidative stress and vigorous variance can result in transforming an acute kidney injury to chronoc kidney disease(CVD).(167) coriander leaf extract contributes to powerful resistance to oxidative stress in the kidney, probably via decreased concentrations in heavy metals. It is likely that decrease in arsenic concentration to the detection limit is a major factor for the resistance.(168) Patients suffering from CKD are often at risk of developing Cardiovascular diseases. Oxidative stress induced inflammation along with obesity are some of the factors that can cause cardiovascular problems. Imbalance of Iron hemostasis often results in renal anemia in these patients which are overcome by iron intake, which in excessive amount that can cause an increase in ROS and oxidative stress. The use of erythropoiesis-stimulating agents (ESAs) may be effective however it needs to be tested in clinical trial.(169)

3.6 Exogenous sources to balance the oxidative stress

Human body has the natural ability to maintain the redox hemostasis via enzymatic and nonenzymatic molecules. However, besides these natual antioxidant species of defense mechanism there are sources that can introduced into the body through diet or external supplementation to counteract the oxidative stress. These species are known as endogenous sources. The exogenous sources are plant-based isolates as discussed above or nutritional anti-oxidants like vitamin E.

3.6.1 Flavonoid's

Flavonoids a class of secondary metabolites, consist of a benzopyrone ring bearing a phenolic or poly phenolic group at different positions, it has a phytochemical constituent which gives it its biological activities. Flavonoid acts as exogenous antioxidant which acts through three different ways. It is directly oxidized by radical to form less reactive specie, by inhibiting nitric-oxide synthase activity, xanthine oxidase activity through its enzyme inhibition, modulation of channel pathways or by interacting with other enzyme systems(170, 171). Chrysoeriol was isolated from the leaves Cardiospermum halicacabum in vitro and tested its antioxidant . Diabetes pathogensis has been reported to be due to OS among other risk factors. The high level of glucose innonenzymatic and auto-oxidative glycosylation, increase polyol and hexosamine pathway, promote protein kinase-C activation and lead to alterations in the levels of inflammatory mediators, as well as in the status of antioxidant defense. These pathways involved in ROS production in diabetic state which directly contribute to the increase of OS in various organs and tissues. The intraperitoneal injection of STZ antibiotic induced diabetes in rats due to its toxic effect on Beta cells of pancreases. This toxicity is associated with ROS production and associated oxidative stress. This causes the lipid peroxidation products to increase in diabetic mice. Antioxidants agents reduce this oxidation by a number of mechanisms which may follow either the ROS scavenging enzyme or non enzyme. The presence of phytonutrients of natural occuuring compounds such as fruits and vegetable acts agains ROS species making it a naturally therapeutic agent. To test the effect of natural extract of Chrysoeriol was administered to diabetic rats and results were determined which indicated that the extract improved the body weight of rats as compare to that of control which displayed its ability to be decrease hyperglycermic CS may exert antioxidant activities and protect the tissues from the LPO.(172)

Bamboo leaf flavonoid extract also indicated a reduction in oxidative stress when the extract was introduced to a sample containing HepG2 cells . The total flavonoid content of the extract was determined to be 78.83 \pm 0.23 mg CE/g dwb with the recognized characteristic components as orientin, isoorientin, vitexin, and isovitexin. Oleic acid concentration was optimized to induce the oxidative stress in HepG2 cells. The cell damage model suggested a concentration of 0.2 mM was enough to effectively damage the cell without causing the cytotoxic effect. The incubated oleic acid was effective in decreasing the Total Antioxidant Capacity Colorimetric (T-AOC) . The formation of ROS was found to be lower (P < 0.05) when OA12+BFE12 samples was used. The extract significantly decreased the ROS production oxidative stress induced by oleic acid and florescence intensity. The mitochondrial membrane potential (MMP) was also found to be lowered when treated with extract. This improvement in MMP contributed in the release of regulatory proteins, such as cytochrome which is also associated with the initiation of apoptosis. Cyt C expression of oleic acid samples was dramatically increased and decreased by BFE intervention (P < 0.05), indicating the alleviation of the apoptosis induced by the BFE intervention(173)

Increased oxidative stress is commonly during pregnancy. The outer layer of blastocyst are a type of cells knowns as trophoblast. Its invasion occur in oxygen deficient environment uterine spiral arterioles are blocked by endovascular trophoblast cells which will cause the spiral arties to dilate by the action of vasodilator substance along with putting it in a state of high-flow low resistance" vessels. This time of oxygen deficient environment also generates ROS which are not good for the developing fetus thus the natural antioxidant are usually recommended. Therefore a study was conducted determine the effect of dietary flavonoids (quercetin, and hesperidin) and their respective metabolites (quercetin-3- glucoside (Q3G) and hesperetin) against hypoxia/reoxygenation-induced oxidative stress in the transformed human first trimester placental cell line HTR-8/SVneo. The results demonstratedconsumption of certain foods containing bioactive compounds (flavonoids) might be beneficial for placental health and invasion.(174)

Flavanols of Ulmus wallichiana were tested on neuron that were treated with lipopolysaccharide, which upon this treatment generates ROS, cytotoxicity, cytochrome c translocation, BCl2 decreased level, increased level of Bax and cleaved caspase-3 in neuronal cells reflecting the involvt UA acts through mitochondria and exhibited its anti-oxidative and anti-apoptotic activities in neuronal cells while no significant anti-inflammatory activity and effect on iNOS were observed(175)ement of intrinsic apoptotic pathway in neuronal death which was improved with UA treatment

Cinnamon is a well-known traditional medicine with antioxidant potential. cinnamaldehyde and its analogues in cinnamon are weak inhibitors of oxidative stress, and thus we speculate that there are novel and/or potent molecules inhibiting oxidative stress in cinnamonCinnamon improved the intracellular antioxidant capacity. A systemic phytochemical investigation of cinnamon gave the isolation of twenty-two chemical ingredients. The purified constituents were tested for their potential inhibitory effects against oxidative stress. Besides cinnamaldehyde analogues, a lignan pinoresinol (PRO) and a flavonol (-)-(2R,3R)-5,7-dimethoxy-3', 4'-methylenedioxy-flavan-3-ol (MFO) were firstly identified to be inhibitors of oxidative stress. Further study indicated that PRO and MFO activated Nrf2-mediated antioxidant response, and protected human lung epithelial cells against sodium arsenite [As(III)]-induced oxidative insults. Conclusion: The lignan PRO and the flavonoid MFO are two novel Nrf2 activators protecting

tissues against oxidative insults, and these two constituents support the application of cinnamon as an agent against oxidative stress related diseases.(176)

Flavanoid troxerutin play a potential role in decreasing hypertension, oxidative stress and dyslipidemia in hypertensive rats. (177) Catechins are a type of phenolic compounds very abundant in tea, cocoa and berries valuate the effects of catechin on cytochrome P450 2E1 (CYP2E1)-dependent oxidative stress. Microsomes co-expressing human CYP2E1 with NADPH cytochrome P450 reductase and cytochrome b5 were incubated with NADPH and DTPA at pH 7.0. Superoxide anion generation was specifically detected by spin-trapping with DEPMPO. Generation of the DEPMPO-OOH adduct was not observed in the absence of CYP2E1 and in the presence of superoxide dismutase (SOD) or catechin, while catalase was ineffective. Reactive 1-hydroxy-3-carboxy-2,2,5,5oxygen species generation was detected with tetramethylpyrrolidine (CPH) by the EPR-detection of its oxidation product, 3-carboxy-proxyl radical (CP•). CP• generation was not observed in the absence of CYP2E1 and in the presence of SOD, while catalase was ineffective. In contrast, catechin increased CPH oxidation, an effect that was not observed in the absence of CYP2E1 or in the presence of SOD (but not catalase), and was not associated with an increase in oxygen consumption. Catechin also increased the non-specific oxidation of the probes CPH and hydroethidine by the superoxide anion-generating system xanthine plus xanthine oxidase. Catechin oxidized CPH in the presence of horseradish peroxidase plus hydrogen peroxide, a catechin radical-generating system. In conclusion, catechin exhibits both antioxidant (superoxide-scavenging) and pro-oxidant effects under CYP2E1dependent oxidative stress.(178)

Amyloid- β peptide (A β) initiates a cascade of pathological events, including activation of microglial cells, oxidative stress, and inflammation, leading to neuronal death and the typical pathological changes in Alzheimer's disease (AD). Flavonoids have been reported to exert neuroprotective activities, not only through their generally accepted antioxidant effects, but also through their ability to protect against neurotoxin-induced injury. Flavonoids reduce Aß production, inhibit neuroinflammation, increase cerebrovascular function, and improve cognitive performance. Here, we analyzed the effects of a flavonoid-rich ethanol extract from the leaves of Diospyros kaki (FLDK) in APP/PS1 transgenic mice. We found that oral treatment with FLDK reversed learning and memory impairment, reduced Aβ burden and expression of β-site amyloid precursor protein cleavage enzyme 1 (BACE1), and decreased microglial activation in senile plaques. FLDK restored antioxidant enzyme activities, as well as reduced the lipid peroxidation product, malondialdehyde, and inflammatory mediators. These results demonstrate that FLDK alleviates cognitive decline and reduces A^β burden, microglial activation, oxidative stress, and inflammation responses. Thus, FLDK treatment may be a potential therapeutic strategy for preventing and treating AD, at least in part via its anti-oxidant and anti-inflammatory biological activities and its effect on the AB producing enzyme BACE1.(179) Hesperetin, a citrus flavonoid, attenuates testicular damage in diabetic rats via inhibition of oxidative stress, inflammation, and apoptosis.(180) Apigenin, a dietary flavonoid, induces apoptosis, DNA damage, and oxidative stress in human breast cancer MCF-7 and MDA MB-231 cells(181) Effect of the flavonoid baicalin on the proliferative capacity of bovine mammary cells and their ability to regulate oxidative stress(182)

3.6.2 Vitamins

Besides flavonoids vitamins also play a role in reduction of oxidative stress. The following



diagram (figure 2) give a detail of some of vitamins that can used to control oxidative stress.

4 Conclusion

It is well accepted that oxidative stress induced diseases ranging from cancer to cardiovascular and kidney diseases are harmful to human body and are a major cause of these diseases.

The use of natural antioxidants and medicinal plant with antioxidant potential has been widely used nowadays because of the ability of these compounds to effectively decrease the oxidative stress as well as not impart any side effects. Thus, we conclude with a statement that oxidative stress is in fact harm to human body however if the proper pathway of this oxidation can be understood fully can be potentially exploited for treatment of oxidative stress induced diseases.

Conflict of interest

Authors share no conflict of interest

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