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Role of Quercetin in DNA Repair and Dysregulated Metabolism. Possible Target to Combat Drug Resistance in Cancer

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ABSTRACT: ONE of the biggest challenges in medicine is finding a remedy for cancer. Earlier to 1950, surgery was thought to be the main form of treatment for cancer. Later, radiation therapy was added as a second method to treat localized tumours. Cancer drug development have modified into billion-dollar industry supported by the advent of novel targeted therapies; however, the basic principles and limitation of chemotherapy are still the same. For instance, chemotherapy is associated with increase psychological distress, fatigue, anxiety accompanied by intense financial distress ultimately causing decrease quality of life. Dietary nutrients, calories limitation and fasting are known to have a large impact in modifying many types of diseases including cancer, and obesity. Quercetin a plant derived flavonoid found abundantly in fruits, vegetables and many beverages possess multiple pharmacological activities shows encouraging potential in treatment and prevention of various types of cancers. Quercetin aglycone has also been shown to modulate several signal transduction pathways involving MEK/ERK and Nrf2/keap1, which are associated with the processes of inflammation and carcinogenesis. Quercetin is an attractive natural compound for cancer prevention due to its beneficial anti-mutagenic and anti-proliferative effects, its strong

antioxidative capacity, and its role in the regulation of cell signaling, cell cycle and apoptosis, all demonstrated in animal and in vitro studies. The aim of the present review is to summarize the key aspects of quercetin role, mechanisms, and future prospects in treating and prevention of cancer by modulating DNA repair, metabolism and drug resistance.

Keywords: Cancer; DNA damage response; Dysregulated Metabolism; Quercetin; Combating Drug Resistance in Cancer.

Abbreviation

G3PDH: Glyceraldehyde-3-phosphate dehydrogenase
PGI: Phoshoglucoisomerase
PFK: Phosphofructokinase
PGK: Phosphosglycearte kinase
HK-II: Hexokinase type II
FA: Fatty acid
SLC27: Solute carrier protein family 27
FABP: Fatty acid binding proteins
ACSS2: Acetyl-CoA synthetase
ACC: Acetyl-CoA carboxylase
DDR: DNA damage response
ATM: Ataxia telangiectasia mutated
ATR: ATM-Rad3 related
EGFR: Epidermal growth factor receptor
FDA: Food and Drug Administration
ABC: ATP-binding cassette
t-**BHP**: tert-butyl hydroperoxide
GST: Glutathione S-transferase
NAC: N-acetylcysteine
NPC1L1: Niemann-Pick C1-like 1
FAS: Fatty acid synthase

1. Introduction

CANCER is a major health concern around the globe. The estimated worldwide data predicts increase rate of cancer in coming decades, with increase rate of mortality and disability (Siegel et al., 2021). The GLOBOCAN 2020 projected that there was 19.29 million cancer cases and 9.96 million of deaths from cancer in year 2020 worldwide (Xia et al., 2022). The number of cancer cases are expected to increase with increase in population, age and adopting lifestyle behaviors such as tobacco use, low physical activity and consumption of unhealthy diet (Torre et al., 2016). Cancer is evaluated by a number of assessments including nature of cancer, risk, prevention and its management (Anand et al., 2008). Cancer involves abnormal growth of mutated cells, rapid cell division and uncontrolled cell proliferation (Galluzzi et al., 2010).

Normal cells divide and proliferate in an organized manner via various metabolic programs. In normal cells, irregular growth is inhibited, when cell came in contact to each other. Mutated or cells with any defect are removed via apoptosis and are replaced with new cells. However, when some cells did not respond to apoptosis due to resistant mutation. The cells replicate abnormally along with mutation resulting in a lump (neoplasm) because of a rapid growth and division. These cells contain broken genetic information. It may invade the normal neighboring cells resulting in a tumor formation. In addition, if it enter the blood circulation it may attack a distant organ leading to tumor metastasis (Kalyanaraman, 2017). However, the tumors which are not cancerous are referred as benign tumors. Benign tumors lack the capacity to metastasize, the possible causes of these types of tumors are associated with genetic disorders, infections, inflammation, occupational stress or intake of toxins etc., (Wang et al., 2018). Cancer is associated with a numerous risk factor often categorized as intrinsic and non-intrinsic risk factors.

The intrinsic factors, which are un modifiable include spontaneous mutation in DNA (due to random error in DNA replication) while the non-intrinsic risk factors are either modifiable and related to exogenous exposures (e.g. infections, carcinogens, smoking, diet, physical activity) or partially modifiable and linked with endogenous risk factors (e.g. metabolism, DNA repair enzyme levels, immune responses)(Wu et al., 2018). The modifiable risk factors are associated with a large

number of organ cancers such as lung, kidney, prostate, skin, stomach colon, cervix oropharynx etc. The literature evidences advocates that these cancers can be prevented if behaviors like cessation of smoking, increase physical activity, reducing body weight, improve quality of diet, limit alcohol drinking and regular screening are encouraged (Stein and Colditz, 2004).

The cure of cancer is one of the big challenges of medicine already passed from many controversies, before 1950 surgery was considered as the primary treatment of cancer later on radiation therapy was added as another approach to treat localize tumors. However, both of these approaches were not sufficient to eradicate the metastatic type of cancer. Therefore the new drugs, biological molecules and combination therapies becomes the central point of research and therapeutics to cure cancer (Chabner and Roberts, 2005).

Cancer drug development have modified into billion-dollar industry supported by the advent of novel targeted therapies; however, the basic principles and limitation of chemotherapy are still the same. For instance, chemotherapy is associated with increase psychological distress, fatigue, anxiety accompanied by intense financial distress ultimately causing decrease quality of life (Groarke et al., 2020; Oh and Cho, 2020). The goal of cancer treatment is to obtain maximum therapeutic response with improved quality of life and minimum adverse effects (Fisusi and Akala, 2019). However, treatment such as chemotherapy have local and systemic side effects on body structure and function involving cardiovascular, mental, respiratory, hematological and immunological systems (Betty Smoot PT et al., 2009). The research advances in nutritional and phytochemistry sciences shows promising evidences that specific phytonutrients induce various genetic expressions demonstrating therapeutic actions to prevent and treat cancer (Bhattacharya et al., 2021).

Dietary nutrients, calories limitation and fasting are known to have a large impact in modifying many types of diseases including cancer, and obesity (Mittelman, 2020). Quercetin a plant derived flavonoid found abundantly in fruits, vegetables and many beverages possess multiple pharmacological activities shows encouraging potential in treatment and prevention of various types of cancers (Batiha et al., 2020). The aim of the present review is to summarize the key aspects of quercetin role, mechanisms, and future prospects in treating and prevention of cancer by modulating DNA repair, metabolism and drug resistance.

2. Dysregulated Metabolism in Cancers

Metabolic alterations are an essential feature of cancerous cells (Hanahan and Weinberg, 2011). The link between metabolism and cancer is multidimensional involving metabolic pathways such as aerobic glycolysis, genetic alteration of metabolic enzymes and reliance on lipid and glutamine metabolism are the few to name. The cancerous cells modify cell metabolism mechanisms in order to accomplish the growing needs of uncontrolled cell proliferation. The principal metabolic pathway that satisfies these needs is glycolysis. Glycolysis pathway involves distinct enzymatic reactions, which converts glucose into pyruvate. Pyruvate is transformed to acetyl co-A or lactate. The former is wholly metabolized to CO_2 and H_2O via tricarboxylic acid (TCA) pathway producing NADH and $FADH_2$ to perform the oxidative phosphorylation (OXPHOS). While the lactate is extruded extracellularly or favored during hypoxia called as aerobic glycolysis (Ganapathy-Kanniappan, 2018; Soto-Heredero et al., 2020). Typically, cancerous cells show increased aerobic glycolysis by converting glucose into lactic acid even in the presence of oxygen. This phenomenon known as Warburg effect (Warburg, 1956). Through this alter mechanism the cancer cell strive to compensate for increased energy demands and other metabolites that are essential for cell survival and proliferation (Hirschey et al., 2015). The continuous aerobic glycolysis results in activation of oncogenes and loss of tumor suppressors causing cancer progression (Jang et al., 2013). A number of enzymes are involved in glycolysis pathway, their expression is increased in cancer cells. The major enzymes includes are hexokinase type II (HK-II), phoshoglucoisomerase (PGI), phosphofructokinase (PFK), aldolase, enolase, phosphosglycearte kinase (PGK), glyceraldehyde-

3-phosphate dehydrogenase (G3PDH) and pyruvate kinase (Akram, 2013; Sreedhar and Zhao, 2018). These enzymes are often involved in non-glycolytic pathways, which contributes to cancer cell proliferation and survival, e.g. HK-II and PGI has anti-apoptotic effect, PGI and G3PDH play its role in survival pathways (Lincet and Icard, 2015). Targeting these enzymes is one of the approaches to treat cancer. Cellular metabolism inhibitors can be combined with chemotherapeutic drugs to treat and reduce drug resistance in cancer (Zhang et al., 2015; Zhao et al., 2013).

Besides aerobic glycolysis increased fatty acid (FA) synthesis is another alter metabolic characteristic of cancer cells. The high amount of FA synthesis helps tumor cells in rapid proliferation, development of cell membrane, which assist both in growth and cells survival. The FA has prominent role as secondary cell messenger to maintain homeostasis and as energy source for cells (Beloribi-Djefaflia et al., 2016). Fatty acids can be synthesized either endogenously or acquired exogenously from diet. Normal well-nourished cells insignificantly depend on *de novo*FA synthesis, conversely its need is fulfilled by exogenous source. However cancer cells pre-dominate *de novo* FA synthesis disregarding the systemic lipid availability(Chen and Huang, 2019). The *de novo* FA synthesis enriches the cancer cell membrane with saturated and mono unsaturated fatty acids, which makes the cells resistant to oxidative stress, drug therapy and lipid peroxidation (Rysman et al., 2010). However, the tumor microenvironment such as hypoxia also plays important role in fatty acid synthesis in many types of cancer, where cancer cells compensate by increase uptake of exogenous lipids (Kamphorst et al., 2013). The exogenous FA uptake are accomplished with the help of specialized transporters such as CD36, solute carrier protein family 27 (SLC27) and plasma membrane fatty acid binding proteins (FABP). In tumors, increase expression of these transporters have been reported (Su and Abumrad, 2009). The increase FA synthesis leads to upregulation of various types of lipogenic enzymes such as ATP citrate lyase (ACLY), acetyl-CoA synthetase (ACSS2), acetyl-CoA carboxylase (ACC), and fatty acid synthase (FASN) (Bhatt et al., 2012; Broadfield et al., 2021; Sreedhar and Zhao, 2018). The upregulated lipogenic enzymes has been reported in various types of cancers such as lung cancer, colorectal cancer, ovarian cancer, gastrointestinal cancer, kidney cancer, prostate cancer, endometrium cancer and skin cancer (Kuhajda, 2000). Different oncogenic signaling pathways plays an important role in regulation of lipid enzymes, for example PI3K-AKT signaling pathways (Fruman et al., 2017), NF-kB (Li et al., 2017), STAT3, MAPK, Wnt/β-catenin and AMPK signaling pathways (Fu et al., 2021). Targeting these enzymes and metabolic pathways is novel and promising therapeutic approach to inhibit cancer cell proliferation, differentiation and metastasis (Sreedhar and Zhao, 2018). However, targeting a single enzyme or signaling pathway is unlikely sufficient to completely cure the dysregulation of FA metabolism. Therefore, the complex framework of FA synthesis should be taken into consideration while designing pharmacological and dietary interventions (Koundouros and Poulogiannis, 2020).

3. Role of DNA repair/ DNA Damage Response in Cancer

There is an established defense system in humans called as DNA repair process or DNA damage response (DDR), which provide protection from exogenous and endogenous geno-toxicants. The DNA repair process protect the genome from various damaging events such as mutations, DNA lesions and genome instability (Kiwerska and Szyfter, 2019). The geno-toxicants agents cause numerous types of DNA damages such as alterations in base pairs, intra-stand or inter-stand cross links, single strand breaks (SSBs), double strand breaks (DSBs), and DNA-protein cross links (Hosoya and Miyagawa, 2014). The DDR identifies and activates specific pathways to repair each type of damage (Goldstein and Kastan, 2015). Briefly the DDR initial response is, recognition of damage via sensor proteins e.g. Ataxia telangiectasia mutated (ATM), ATM-Rad3 related (ATR), and DNA-dependent protein kinases (DNA-PKs) (Lovejoy and Cortez, 2009). After recognition the DDR activates cell cycle checkpoints, cell cycle arrest, transcriptional programs, apoptosis and

immune clearance (Dai and Grant, 2010; McNally et al., 2017). The failure of DNA repair process leads to wide scale genome aberrations causing immuno-deficiencies, neurodegeneration, infertility and increase risk of cancer (Hanahan and Weinberg, 2011; Jackson and Bartek, 2009; Moraes et al., 2012). The accumulating evidence shows that genomic instability caused due to failure in DDR leads to development of cancer pathogenesis by activating a chain of events involving proto-oncogenes stimulation and anti-oncogenes suppression (Ma et al., 2021). The common proto-oncogenes evidenced in such scenario are epidermal growth factor receptor (EGFR), MYC and RAS families, while *TP53* as recognized tumor suppressor gene (Dai et al., 2020; Tosato et al., 2013). The molecular mechanisms that are involved in genome stability and instability are the novel issues, which can be helpful for clinician to design approaches to treat or prevent cancer (Huang and Zhou, 2021). The distinct defective DDR responses are a hallmark of cancer (Jeggo et al., 2016), and underpin novel therapeutic approach to treat cancer (Nickoloff et al., 2017; Snyder et al., 2014). For example, the PARP1/2 inhibitors such as olaparib, nirparib and rucaparib drugs has been approved by the Food and Drug Administration (FDA) of USA for ovarian cancer therapy (Nesic et al., 2018). These agents sense DNA damage and transduce signals to bind with DNA breaks, where it repairs DNA by synthesizing poly (ADP-ribose) (PAR) chains on target proteins (PARylation) and recruitment of other DNA repair effectors (Langelier et al., 2018). The PARP inhibitors have dual mechanism of action; they act as DNA repair inhibitor and also as DNA damaging agent. The DNA damaging action is primarily mediated by the presence of PARP proteins (Murai, 2017). The PARP-DNA complexes are more cytotoxic, it blocks DNA replication and arrest cell cycles in S-phase (Murai et al., 2012). These evidence shows that DNA damage is one of the root cause of cancer development (figure 1), however it also provides new avenues for designing novel chemotherapeutic entities to treat and prevent cancer (Torgovnick and Schumacher, 2015).

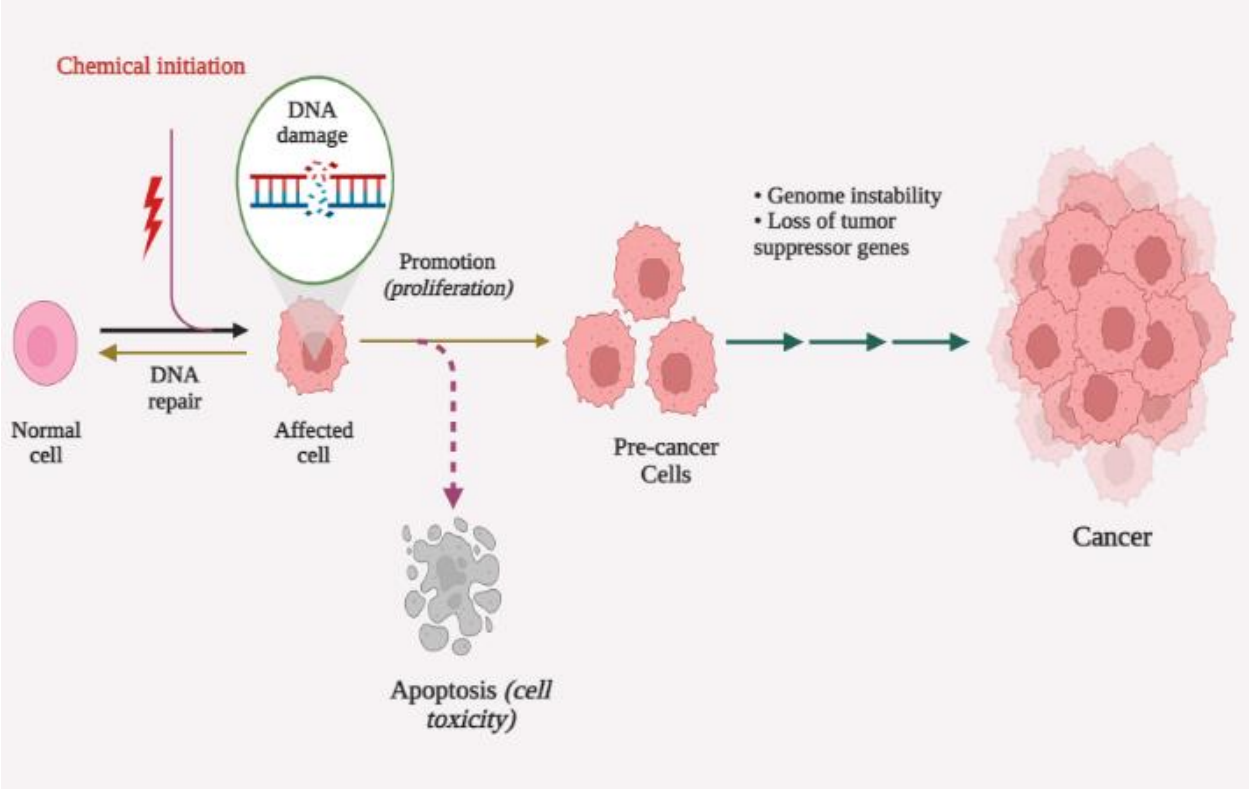

Figure 1: DNA damages leading to cancer pathway.

4. Current Status of Cancer Drug Resistance

Chemotherapy is first line of treatment for most types of cancers, though the drug resistance (DR) to chemotherapy lowers its effectiveness and limits its applications to treat cancer. The DR to chemotherapy is either intrinsic or acquired, the intrinsic DR shows that there are already pre-existing factors in tumors while acquired DR factors are developed during chemotherapy caused by mutations or by cell sensitive pathways (Holohan et al., 2013). Multiple drug resistance mechanisms are responsible for DR including increased drug efflux where increased expression of protein such as ATP-binding cassette (ABC). MDR1 (P-glycoprotein) and multidrug resistance proteins (MRPs) acts as cell membrane transporters and pump out the drug from cancer cells (Robey et al., 2018). Similarly, reduce drug uptake (decrease concentration of drug inside cancer cells) e.g. commonly occurs in case of methotrexate and 5-fluorouracil therapy, drug inactivation mechanism where drug metabolizing enzymes are altered causing DR to therapy, target mutation mechanism where the targeted tumor mutated itself leading to DR, signaling pathway alterations mechanism, phenotype switching and apoptotic defects mechanisms are the common DR mechanisms towards cancer chemotherapy (Ward et al., 2020). Numerous factors are responsible for causing DR to chemotherapy including microenvironment of tumors, heterogeneity of tumors, cancer drivers not responsive towards drugs, immune responses, and tumor burden and growth kinetics (Vasan et al., 2019). Tumor cancer cells are regulated by a complex dynamical system, the knowledge and understanding of specific DR mechanism involved is immensely important, therefore before stating therapy it should be considered thoroughly in order to minimize the risk of DR (Salgia and Kulkarni, 2018). The development of novel therapeutics entities, refining pharmacological principles and monitoring drug therapy according to tumor growth responses are the some of the solutions to cope with DR in cancer (Vasan et al., 2019). The progression of targeted therapies, proteomics and DNA microarray techniques provides new paradigms to surmount the DR (Mansoori et al., 2017). Natural products reverses DR via multiple mechanisms including regulation of drug resistant proteins and targeting non apoptotic cell death programs such as necroptosis, autophagy, methuosis and oncosis (Yuan et al., 2017). Natural products act through multiple pathways producing inhibitory effects on tumors, decrease the adverse effects of chemotherapy, boost the immune responses and improves the quality of life (Guo et al., 2017).

5. Effects of Quercetin on DNA Repair

Day by day we are exposed to chemical carcinogens in the environment, ultraviolet (UV) radiation, ionizing radiation, and also those substances produced in our body during cellular metabolism that attack and produce a variety of DNA injuries. Each lesion favors the development of alterations in DNA and chromosomes, which favors oncogenic transformation and tumor progression. In order to reduce the number of changes in the genome and its instability, cells have several pathways of response to damage and DNA repair proteins that eliminate these lesions (Lagunas-Rangel and Bermúdez-Cruz, 2020). Natural compounds are biologically active substances present in plants, fungi, bacteria, and other organisms that are affective in DNA repair, and are distributed mainly according to their chemical structure into different classes like terpenes, carotenoids, phenolic acids, flavonoids, stilbenes, coumarins, tannins, alkaloids, nitrogen compounds, organosulfates, isothiocyanates and indoles, allyl sulfates. Flavonoids are further divided into chalcones, flavanones, flavones, flavonols, flavanols, isoflavones, and anthocyanins (Lagunas-Rangel and Bermúdez-Cruz, 2020). Flavonoids helps in the prevention of degenerative diseases, including cancer. Quercetin flavonoid in nature used in the concentration ranging from 1 to 100 μM significantly reduced oxidative DNA damage (Min and Ebeler, 2009). Quercetin treatment also caused a measurable increase in the mRNA expression of human 8-oxoguanine DNA glycosylase (hOGG1) at 0 and 4 h after H_2O_2

treatment measured using RT-PCR. This indicates that quercetin could protect DNA both by reducing oxidative DNA damage and by enhancing DNA repair through modulation of DNA repair enzyme expression(Min and Ebeler, 2009). The chemoprotective effects of quercetin on tert-butyl hydroperoxide (t-BHP)-induced DNA damage in a human hepatoma cell line (HepG2) were investigated by the comet assay (Ramos et al., 2008). The results show that quercetin prevented DNA damage and had antiproliferative properties in HepG2 cells suggesting an anticarcinogenic potential for this compound. The protective effect of quercetin against t-BHP-induced DNA damage seem to be due to both direct effects on t-BHP toxicity and to cellularly mediated indirect effects which reflect the potentiation of the cellular antioxidant defenses (Ramos et al., 2008). In hydrogenperoxide-induced DNA damage, quercetin exhibits protective effect in Caco-2, human peripheral blood lymphocytes and murine leukemia cells. These results indicate the protective effect of quercetin on DNA from oxidative attack in vitro (Okamoto, 2005). Mitomycin C is a mutagenic anticancer drug, and inhuman lymphocytes, quercetin displays protection on DNA from mitomycin C-induced damage in a concentration dependent manner in vitro (Ündeğer et al., 2004). Quercetin can possibly exert hepatoprotective and antioxidant activity against acrylamide (ACR) induced toxicity in rats. ACR caused an elevation in 8-OH guanosine level and a reduction in Glutathione S-transferase (GST) activity. Administration of QR significantly protected liver tissue against hepatotoxic effect of acrylamide from amelioration of the marker enzyme and DNA damage as evident by comet assay. It has been observed that ACR induced DNA damage was significantly decreased after the treatment of Quercetin (Ansar et al., 2016). Researcher investigated the protective effect of quercetin against nicotine-induced prooxidant and antioxidant imbalance in circulation, lung, liver, and kidney of experimental rats. The protective effect of quercetin was compared with N-acetylcysteine (NAC), a well-known antioxidant (Muthukumaran et al., 2008). Quercetin is a potent proapoptotic drug that activates both intrinsic and extrinsic apoptotic mechanisms. Quercetin raises intracellular ROS and Ca2+ levels, causing mitochondrial membrane potential to depolarize, cytochrome c to be released, and caspases like caspase 9 and caspase 3 to be activated. Alternatively, quercetin stimulates Bax translocation from the cytosol to the mitochondrial membrane, resulting in depolarization of the mitochondrial membrane potential and, as a result, induction of apoptosis. Bcl-2 and Bcl-XL proteins generally prevent Bax penetration into the mitochondrial membrane (figure 2) (Rather and Bhagat, 2020). The extent of DNA damage evaluated by comet assay was significantly increased in circulatory blood of nicotine-treated rats, which was effectively brought down by quercetin treatment. The protective effect of quercetin against nicotine toxicity was comparable to that of NAC. Experimental data suggest that quercetin exerts its protective effect by modulating the extent of lipid peroxidation and augmenting antioxidant defense system and thus protects the DNA in experimental animals (Muthukumaran et al., 2008).

Generation of superoxide and hydroxyl radicals may lead to DNA damage in Type 2Diabetes Mellites in mice this was tested using the comet assay. The average tail length of the comet, a measure of DNA damage was found to be significantly higher in the diabetic group compared to control. However, quercetin supplementation showed a significant recovery in DNA damage as evident from the decreased average tail length of the comet(Alam et al., 2014). In the US and Europe, quercetin supplements are commercially available. Quercetin has been empirically used for the treatment of disease, and beneficial effects of quercetin in clinical trials were reported. Tyrosine kinase is a target of quercetin inhibiting tumor proliferative activity. Phase I clinical trial of quercetin on the inhibitory effect against tyrosine kinase was reported. The authors recommended the dose of quercetin at 1400 mg/m2, which is equal to 2.5 g/70 kg, as the

bolus intravenous dose given either in 3-week or weekly intervals, for Phase II trials. Improvement of prostatitis and interstitial cystitis by the treatment with a quercetin supplement of 500 mg twice per day for one month was also reported (Okamoto, 2005).

6. Effects of Quercetin on dysregulated metabolism

Plants and plant parts are used for its scent, flavor, or therapeutic properties. There are a number of advantages associated with using plants and plant phytoconstituents as opposed to pharmaceutical products. Flavonoids have existed over one billion years and possess wide spectrum of biological activities that might be able to influence processes which are dysregulated in a disease. Quercetin is one of the important bioflavonoids play a vital role in the regulation of metabolic disorders (David et al., 2016). Many investigators have shown that quercetin has good pharmacological activity on hyperlipidemia. It could reduce the levels of TG, TC, LDL, and VLDL. Quercetin treatment reduced serum TC, TG, and LDL levels by 30%, 34%, and 22%, respectively (Yi et al., 2021). Juzwiak *et al* studied the effect of quercetin on experimental hyperlipidemia in rabbits. The results demonstrated that quercetin taken for 12 weeks could effectively reduce serum TG and cholesterol levels elevated by high-fat diet (JuŸwiak et al., 2005). Moreover, quercetin could decrease plasma cholesterol and prevent the hypertrophy of the left ventricular in hypercholesterolemic mice (Ulasova et al., 2013). The mechanism of quercetin's antihyperlipidemic effect may involve multiple aspects.

Quercetin could reduce high blood cholesterol levels by specifically inhibiting the absorption of intestinal cholesterol through reducing the expression of the epithelial cholesterol transporter Niemann-Pick C1-like 1 (NPC1L1) (Yi et al., 2021). Jung *et al* and Kobori*et al* found that quercetin supplementation improved dyslipidemia through reducing oxidative stress, increasing PPARα expression, and improving the expression of some genes related to lipid metabolism in mice, including farnesyltransferase CAAX box α (Fnta), paraoxonase 1 (Pon1), aldehyde dehydrogenase 1 family member B1 (Aldh1b1), ATP-binding cassette subfamily G member 5 (Abcg5), apolipoprotein A-IV (Apoa4), acetyl-coenzyme A carboxylase α (Acaca), fatty acid synthase (FAS), cluster of differentiation 36 (CD36), glycerol-3-phosphate acyltransferase mitochondrial (Gpam), and sterol regulatory element-binding protein-1c (SREBP-1c) (Jung et al., 2013), (Kobori et al., 2011). Another study indicated that quercetin might treat hyperlipidemia by promoting PPARγ and liver X receptor α (LXRα) expressions to upregulate ATP-binding cassette transporter A1 (ABCA1) genes and increasing cholesterol efflux from THP-1 macrophages in human acute monocytic leukemia cells (Lee et al., 2013). Quercetin upregulated genes involved in mitochondrial biogenesis and oxidative metabolism in lipid-laden hepatocytes and the livers of HFD-fed obese mice, and this was accompanied by increased levels of the transcription factor, nuclear erythroid 2-related factor 2 (Nrf-2), and HO-1 protein. The HO-1 inducer hemin and the HO-1 by product carbon monoxide (CO) also enhanced hepatic oxidative metabolism in HFD-fed obese mice. Moreover, the metabolic changes and the lipid-lowering effects of quercetin were completely blocked by the HO-1 inhibitor ZnPP and by deficiency of Nrf-2. These findings suggest that quercetin stimulates hepatic mitochondrial oxidative metabolism by inducing HO-1 via the Nrf-2 pathway. The experimental model was Male C57BL/6 mice that were fed a regular diet (RD), a high-fat diet (HFD), and an HFD supplemented with quercetin for 9 weeks. Levels of mitochondrial biogenesis and oxidative metabolic transcripts/proteins were measured by real-time PCR and/or Western blotting. HO-1 transcripts/proteins were measured real-time PCR and/or Western blotting(Kim et al., 2015).Quercetin evidently down regulated expression of LDLr, HMGCR, SREBP-2, and SCAP subsequently attenuated the renal lipid

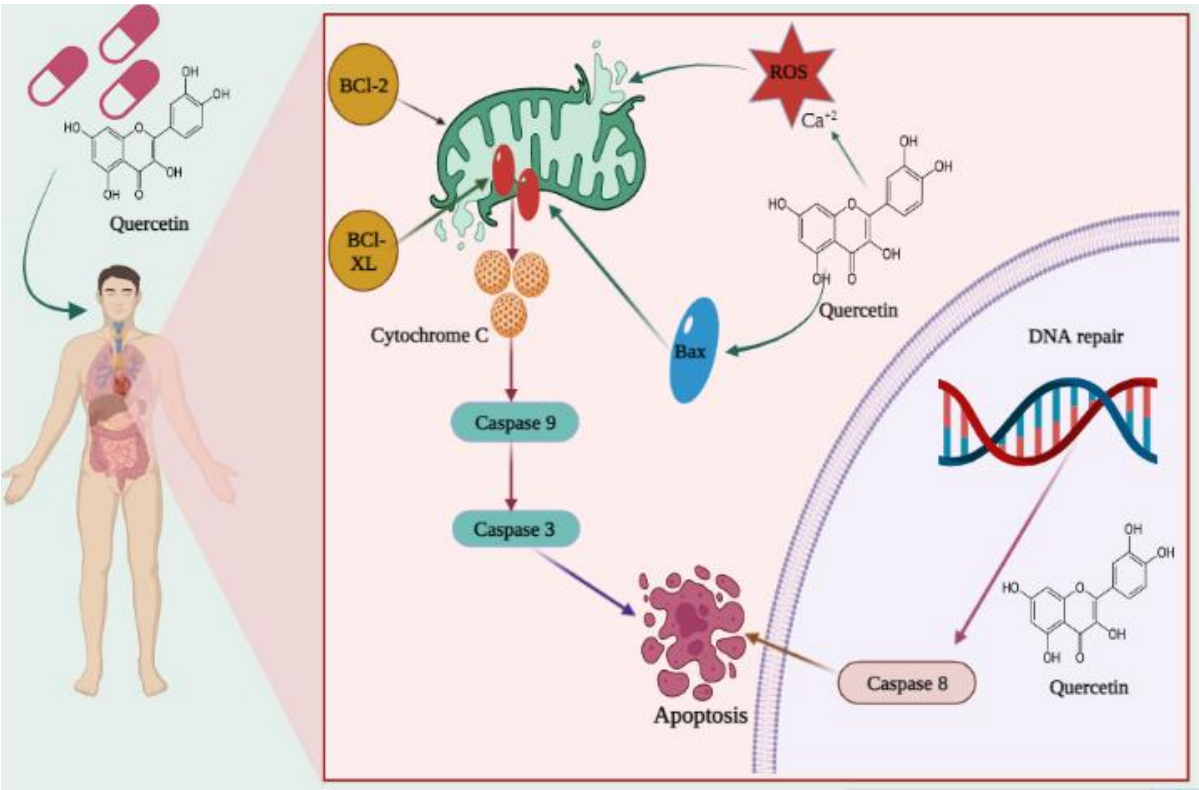

Figure 2: Schematic representation of mechanism of action of Quercetin induced apoptosis and DNA repair response.

profile change and lipid droplet accumulation, resulting in the alleviation of renal injury of db/db mice. Quercetin possibly improving the lipid metabolism via SCAP-SREBP2-LDLr signaling pathway (Jiang et al., 2019). Treatment with quercetin reduced AKT phosphorylation and oxidative/nitrosative stress, inflammation and lipid metabolism-related genes displayed a tendency to normalize in both in vivo and in vitro models. These results put quercetin as a potential therapeutic strategy for preventing NAFLD progression by attenuating gene expression deregulation, at least in part through PI3K/AKT pathway inactivation (Pisonero-Vaquero et al., 2015). Rapid expansion of visceral adipose tissue which leads to a profound change of gene expression in adipocytes. As a consequence, there is a dysregulation of metabolism and adipokine secretion. Influence of quercetin on human SGBS (Simpson Golabi Behmel Syndrome) adipocytes' gene expression for the first time it is revealed that quercetin significantly changed expression of adipokine (Angptl4, adipsin, irisin and PAI-1) and glycolysis-involved (ENO2, PFKP and PFKFB4) genes, and that this effect not only antagonized but in part even overcompensated the effect mediated by hypoxia in adipocytes. Thus, these results are explained by the recently proposed hypothesis that the protective effect of quercetin is not solely due to its free radical-scavenging activity but also to a direct effect on mitochondrial processes, and they demonstrate that quercetin might have the potential to counteract the dysregulated metabolic complications (Leiherer et al., 2016).

7. Effect of quercetin on possible target to combat drug resistance in cancer

Scambia, G., et al showed that the flavonoid quercetin, a plant-derived compound with low toxicity in vivo, greatly potentiates the growth-inhibitory activity of Adriamycin (ADR) on

MCF-7 ADR-resistant human breast cancer cells. The effect of quercetin was dose-dependent at concentrations ranging between 1 and 10 μM. Since ADR resistance in these cells is associated with the expression of high levels of P-glycoprotein (Pgp), we evaluated the effect of quercetin and related flavonoids of Pgp activity in cytofluorographic efflux experiments with the fluorescent dye rhodamine 123 (Rh 123) (Scambia et al., 1994). The results indicate that quercetin and 3-OMe quercetin (3′,4′,7-trimethoxyquercetin) but not the 3-rhamnosylglucoside of quercetin (rutin) inhibit the Pgp pump-efflux activity in a dose-related manner. Moreover, 10 μM quercetin reduces the expression of the immunoreactive Pgp in MCF-7 ADR-resistant cells as evaluated by cytofluorimetric assay. These findings provide a further biological basis for the potential therapeutic application of quercetin as an anticancer drug either alone or in combination with ADR in multidrug-resistant breast tumor cells (Scambia et al., 1994). Borska, S., et al., suggest that flavonoid quercetin induces lethal effect in many types of tumors and may sensitize resistant cells to drugs. The aim of study was to examine the effect of quercetin on human gastric carcinoma cells and to determine mode of its action. The parental EPG85-257P cell line and its daunorubicin-resistant variant EPG85-257RDB were used as cell models (Borska et al., 2012).

The data revealed that quercetin exerted antiproliferative impact on studied cells (with IC50 value of 12 μM after 72 h), mainly through induction of apoptosis. In sensitive cells cytostatic drug and flavonoid had synergistic effects, in EPG85-257RDB cells quercetin acted as a chemosensitizer. Its impact on resistance mechanism involved decrease of P-glycoprotein expression, inhibition of drug transport and downregulation of ABCB1 gene expression. These findings demonstrate that quercetin may be considered as a prospective drug to overcome classical resistance in gastric cancer cells (Borska et al., 2012). Chen, Z., et al., aimed a study to investigate the reversal effect of quercetin on multi drug resistance (MDR) and explored its mechanism of action in vitro. The effect and mechanism of quercetin on MDR was examined by using MTT assay, flow cytometry, real-time PCR, and western blot analysis in human hepatocellular carcinoma cells (Chen et al., 2018). From the data it has been observed that the intracellular accumulation of rhodamine-123 (Rh123) and doxorubicin (ADR) were increased, the sensitivity of BEL/5-FU cells to chemotherapeutic drugs were increased, and the expressions of ABCB1, ABCC1 and ABCC2 were all down-regulated, which indicated that the functions and expressions of ABCB1, ABCC1 and ABCC2 efflux pump were inhibited by quercetin treatment. Moreover, the suppression of ABCB1, ABCC1 and ABCC2 by quercetin was dependent on the FZD7 through the Wnt/β-catenin pathway(Chen et al., 2018). Further research revealed that reduction of FZD7 by RNA interference (siFZD7) enhanced the sensitivity to chemotherapeutic drugs, increased the cellular accumulation of Rh123 and ADR, and induced inhibitory effects on the expression of FZD7, ABCB1, ABCC1, ABCC2 and β-catenin, similar to quercetin. In the meanwhile, overexpression of FZD7 showed the inverse effect on the expressions. Interesting, it was confirmed that quercetin could inhibit the expression levels of FZD7, ABCB1, ABCC1, ABCC2 and β-catenin in BEL-7402 cells; furthermore, treatment by quercetin combined with siFZD7 in BEL/5-FU cells, the expressions of these genes were effectively decreased in comparison to quercetin combined with siRNA negative control (sncRNA).Overall, these data suggested the effectiveness of using quercetin, at least in part, via inhibiting FZD7 to combat chemoresistance and showed that quercetin could be developed into an efficient natural sensitizer for resistant human hepatocellular carcinoma (Chen et al., 2018).

Chemotherapy plays crucial roles in the clinical treatment of non-small cell lung cancer (NSCLC). Nevertheless, acquired chemoresistance is a common and critical problem that limits the clinical application of chemotherapy. Wang, Y., et al., showed that Quercetin (QUE), a natural bioflavonoid, has significant antitumor potential,

which has been verified in many drug-resistant cancer cell lines and animal models. Here, we explored whether QUE could reverse the resistance of NSCLC to paclitaxel (PTX)-based therapy.

The results of cell viability revealed that QUE could synergistically enhance the cytotoxicity of PTX in A549 and A549/Taxol cells (Wang et al., 2021). Furthermore, Akt and ERK phosphorylation had no significant changes in A549/Taxol cells treated with PTX. However, it was significantly inhibited by the combination treatment of QUE and PTX. To improve the antitumor activity of PTX due to its hydrophobicity and eliminate its toxicity, we prepared targeted biodegradable cetuximab chitosan nanoparticles (Cet-CTS NPs) to deliver PTX and QUE using ionic cross-linking technique. The targeted NPs displayed a particle size of 290 nm and sustained release of PTX and QUE. In addition, the targeted Cet-CTS NPs loaded with PTX, and QUE inhibited tumor growth in PTX-resistant A549/Taxol cells. Cet-QUE NPs decreased tumor growth in PTX-resistant xenografts. In conclusion, the administration of QUE by using Cet-CTS NPs could provide a prospective strategy for the treatment of PTX-resistant lung cancer(Wang et al., 2021). Among the flavonoids in the human diet, quercetin is one of the most important. In the last decades, several anticancer properties of quercetin have been described, such as cell signaling, pro-apoptotic, anti-proliferative and antioxidant effects, growth suppression. In fact, it is now well known that quercetin has diverse biological effects, inhibiting multiple enzymes involved in cell proliferation, as well as in signal transduction pathways (Filipa Brito et al., 2015). On the other hand, there are also studies reporting potential synergistic effects when combined quercetin with chemotherapeutic agents or radiotherapy. In fact, several studies which aim to explore the anticancer potential of these combined treatments have already been published, the majority with promising results. It is well known that quercetin can act on the chemo sensitization and radio sensitization but also as chemoprotective and radioprotective, protecting normal cells of the side effects that result from chemotherapy and radiotherapy, which obviously provides notable advantages in their use in anticancer treatment. Thus, all these data indicate that quercetin may have a key role in anticancer treatment and also in chemoresistance by acting on multiple targets which are already described above in this review article (Filipa Brito et al., 2015).

8. Discussion and Future Prospects

Quercetin is an important flavonol among the members of six subclasses of flavonoid compounds. The name quercetin was derived from quercetum (after Quercus, i.e., oak), and has been used since 1857.It has been named as 3,3′,4′,5,7-pentahydroxyflavone by the International Union of Pure and Applied Chemistry (IUPAC). It is also known by its synonym 3,3′,4′,5,7-pentahydroxy-2-phenylchromen-4-one. Quercetin is the most widely distributed and extensively studied flavonoid found in various food sources, including fruits, vegetables, nuts, wine, and seeds. Quercetin has various biological properties, including antioxidant, anti-inflammatory, antibacterial, antiviral, radical-scavenging, gastro protective, and immune-modulatory activities (Kim and Park, 2018).

The bioavailability of quercetin, including its intestinal absorption and metabolic conversion, needs to be understood in order to estimate the efficacy of its anti-carcinogenic effect. It has long been known that quercetin disappears immediately from the plasma when administered intravenously to rodents. This suggests that quercetin is metabolized rapidly and excreted into the urine with no accumulation in tissues and biological fluids. It has previously also been believed that dietary quercetin was excreted into the feces without intestinal absorption, but recent studies have shown that a considerable amount of dietary quercetin can be absorbed from the digestive tract and undergo subsequent metabolic conversion (Murota et al., 2000). Phenolic hydroxyl groups at the B-ring and the 3-position are responsible for its free radical-scavenging activity.

Quercetin is commonly present as a glycoside and is converted to glucuronide/sulfate conjugates during intestinal absorption and only conjugated metabolites are therefore found in circulating blood. Although metabolic conversion attenuates its biological effects, active aglycone may be generated from the glucuronide conjugates by enhanced β-glucuronidase activity during inflammation (Murakami et al., 2008). With respect to its relationship with molecular targets relevant to cancer prevention, quercetin aglycone has been shown to interact with some receptors, particularly an aryl hydrocarbon receptor, which is involved in the development of cancers induced by certain chemicals. Quercetin aglycone has also been shown to modulate several signal transduction pathways involving MEK/ERK and Nrf2/keap1, which are associated with the processes of inflammation and carcinogenesis. Rodent studies have demonstrated that dietary administration of this flavonol prevents chemically induced carcinogenesis, especially in the colon, whilst epidemiological studies have indicated that an intake of quercetin may be associated with the prevention of lung cancer.

Dietary quercetin is, therefore, a promising agent for cancer (Murakami et al., 2008).Quercetin is an attractive natural compound forcancer prevention due to its beneficial anti-mutagenicand anti-proliferative effects, its strong antioxidativecapacity, and its role in the regulation ofcell signaling, cell cycle and apoptosis, all demonstratedin animal and in vitro studies. However, metabolic conversion must be taken into accountwhen estimating the bioavailability and efficacy ofquercetin for pharmacological use. The conjugationof xenobiotics attenuates their reactivity, but nevertheless,some conjugated metabolites of quercetinpossess biological activity and active aglycone maybe generated by the site-specific activation of hydrolyticenzymes. Numerous molecular targets havebeen proposed to account for the chemopreventiveeffects of quercetin aglycone. Further investigation into the modes of action of polyphenols will require the analysis of data derived from experimental,in vitro studies, which will help to identify the novel mechanisms whereby quercetin suppresses rodentcarcinogenesis (Murakami et al., 2008).

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REFERENCES

Akram, M., 2013. Mini-review on glycolysis and cancer. J. Cancer Educ. 28, 454-457.

Alam, M.M., Meerza, D., Naseem, I., 2014. Protective effect of quercetin on hyperglycemia, oxidative stress and DNA damage in alloxan induced type 2 diabetic mice. Life sciences 109, 8-14.

Anand, P., Kunnumakara, A.B., Sundaram, C., Harikumar, K.B., Tharakan, S.T., Lai, O.S., Sung, B., Aggarwal, B.B., 2008. Cancer is a preventable disease that requires major lifestyle changes. Pharm. Res. 25, 2097-2116.

Ansar, S., Siddiqi, N.J., Zargar, S., Ganaie, M.A., Abudawood, M., 2016. Hepatoprotective effect of Quercetin supplementation against Acrylamide-induced DNA damage in wistar rats. BMC complementary and alternative medicine 16, 1-5.

Batiha, G.E.-S., Beshbishy, A.M., Ikram, M., Mulla, Z.S., El-Hack, M.E.A., Taha, A.E., Algammal, A.M., Elewa, Y.H.A., 2020. The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: Quercetin. Foods 9, 374.

Beloribi-Djefaflia, S., Vasseur, S., Guillaumond, F., 2016. Lipid metabolic reprogramming in cancer cells. Oncogenesis 5, e189-e189.

Betty Smoot PT, D., Meredith Wampler PT, D., Topp, K.S., 2009. Breast cancer treatments and complications: implications for rehabilitation. Rehabil. Oncol. 27, 16.

Bhatt, A.P., Jacobs, S.R., Freemerman, A.J., Makowski, L., Rathmell, J.C., Dittmer, D.P., Damania, B., 2012. Dysregulation of fatty acid synthesis and glycolysis in non-Hodgkin lymphoma. Proceedings of the National Academy of Sciences 109, 11818-11823.

Bhattacharya, T., Dutta, S., Akter, R., Rahman, M.H., Karthika, C., Nagaswarupa, H.P., Murthy, H.C.A., Fratila, O., Brata, R., Bungau, S., 2021. Role of Phytonutrients in Nutrigenetics and Nutrigenomics Perspective in Curing Breast Cancer. Biomolecules 11, 1176.

Borska, S., Chmielewska, M., Wysocka, T., Drag-Zalesinska, M., Zabel, M., Dziegiel, P., 2012. In vitro effect of quercetin on human gastric carcinoma: targeting cancer cells death and MDR. Food and chemical toxicology 50, 3375-3383.

Broadfield, L.A., Pane, A.A., Talebi, A., Swinnen, J.V., Fendt, S.-M., 2021. Lipid metabolism in cancer: New perspectives and emerging mechanisms. Dev. Cell 56, 1363-1393.

Chabner, B.A., Roberts, T.G., 2005. Chemotherapy and the war on cancer. Nature Reviews Cancer 5, 65-72.

Chen, M., Huang, J., 2019. The expanded role of fatty acid metabolism in cancer: new aspects and targets. Precision Clinical Medicine 2, 183-191.

Chen, Z., Huang, C., Ma, T., Jiang, L., Tang, L., Shi, T., Zhang, S., Zhang, L., Zhu, P., Li, J., 2018. Reversal effect of quercetin on multidrug resistance via FZD7/β-catenin pathway in hepatocellular carcinoma cells. Phytomedicine 43, 37-45.

Dai, X., Huang, R., Hu, S., Zhou, Y., Sun, X., Gui, P., Yu, Z., Zhou, P., 2020. A novel miR-0308-3p revealed by miRNA-seq of HBV-positive hepatocellular carcinoma suppresses cell proliferation and promotes G1/S arrest by targeting double CDK6/Cyclin D1 genes. Cell & bioscience 10, 1-18.

Dai, Y., Grant, S., 2010. New Insights into Checkpoint Kinase 1 in the DNA Damage Response Signaling NetworkChk1 as an Anticancer Target. Clin. Cancer Res. 16, 376-383.

David, A.V.A., Arulmoli, R., Parasuraman, S., 2016. Overviews of biological importance of quercetin: A bioactive flavonoid. Pharmacognosy reviews 10, 84.

Filipa Brito, A., Ribeiro, M., Margarida Abrantes, A., Salome Pires, A., Jorge Teixo, R., Guilherme Tralhao, J., Filomena Botelho, M., 2015. Quercetin in cancer treatment, alone or in combination with conventional therapeutics? Current medicinal chemistry 22, 3025-3039.

Fisusi, F.A., Akala, E.O., 2019. Drug combinations in breast cancer therapy. Pharmaceutical nanotechnology 7, 3-23.

Fruman, D.A., Chiu, H., Hopkins, B.D., Bagrodia, S., Cantley, L.C., Abraham, R.T., 2017. The PI3K pathway in human disease. Cell 170, 605-635.

Fu, Y., Zou, T., Shen, X., Nelson, P.J., Li, J., Wu, C., Yang, J., Zheng, Y., Bruns, C., Zhao, Y., 2021. Lipid metabolism in cancer progression and therapeutic strategies. MedComm 2, 27-59.

Galluzzi, L., Morselli, E., Kepp, O., Vitale, I., Rigoni, A., Vacchelli, E., Michaud, M., Zischka, H., Castedo, M., Kroemer, G., 2010. Mitochondrial gateways to cancer. Mol. Aspects Med. 31, 1-20.

Ganapathy-Kanniappan, S., 2018. Molecular intricacies of aerobic glycolysis in cancer: current insights into the classic metabolic phenotype. Crit. Rev. Biochem. Mol. Biol. 53, 667-682.

Goldstein, M., Kastan, M.B., 2015. The DNA damage response: implications for tumor responses to radiation and chemotherapy. Annu. Rev. Med. 66, 129-143.

Groarke, A., Curtis, R., Skelton, J., Groarke, J.M., 2020. Quality of life and adjustment in men with prostate cancer: Interplay of stress, threat and resilience. PLoS One 15, e0239469.

Guo, Q., Cao, H., Qi, X., Li, H., Ye, P., Wang, Z., Wang, D., Sun, M., 2017. Research progress in reversal of tumor multi-drug resistance via natural products. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents) 17, 1466-1476.

Hanahan, D., Weinberg, R.A., 2011. Hallmarks of cancer: the next generation. Cell 144, 646-674.

Hirschey, M.D., DeBerardinis, R.J., Diehl, A.M.E., Drew, J.E., Frezza, C., Green, M.F., Jones, L.W., Ko, Y.H., Le, A., Lea, M.A., 2015. Dysregulated

metabolism contributes to oncogenesis, Semin. Cancer Biol. Elsevier, pp. S129-S150.

Holohan, C., Van Schaeybroeck, S., Longley, D.B., Johnston, P.G., 2013. Cancer drug resistance: an evolving paradigm. Nature Reviews Cancer 13, 714-726.

Hosoya, N., Miyagawa, K., 2014. Targeting DNA damage response in cancer therapy. Cancer Sci. 105, 370-388.

Huang, R., Zhou, P.-K., 2021. DNA damage repair: Historical perspectives, mechanistic pathways and clinical translation for targeted cancer therapy. Signal Transduction and Targeted Therapy 6, 1-35.

Jackson, S.P., Bartek, J., 2009. The DNA-damage response in human biology and disease. Nature 461, 1071-1078.

Jang, M., Kim, S.S., Lee, J., 2013. Cancer cell metabolism: implications for therapeutic targets. Exp. Mol. Med. 45, e45-e45.

Jeggo, P.A., Pearl, L.H., Carr, A.M., 2016. DNA repair, genome stability and cancer: a historical perspective. Nature Reviews Cancer 16, 35-42.

Jiang, X., Yu, J., Wang, X., Ge, J., Li, N., 2019. Quercetin improves lipid metabolism via SCAP-SREBP2-LDLr signaling pathway in early stage diabetic nephropathy. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 12, 827.

Jung, C.H., Cho, I., Ahn, J., Jeon, T.I., Ha, T.Y., 2013. Quercetin reduces high-fat diet-induced fat accumulation in the liver by regulating lipid metabolism genes. Phytotherapy Research 27, 139-143.

JuŸwiak, S., Wójcicki, J., Mokrzycki, K., Marchlewicz, M., Białecka, M., Wenda-Różewicka, L., Gawrońska-Szklarz, B., Droździk, M., 2005. Effect of quercetin on experimental hyperlipidemia and atherosclerosis in rabbits. Pharmacol Rep 57, 604-609.

Kalyanaraman, B., 2017. Teaching the basics of cancer metabolism: Developing antitumor strategies by exploiting the differences between normal and cancer cell metabolism. Redox Biology 12, 833-842.

Kamphorst, J.J., Cross, J.R., Fan, J., De Stanchina, E., Mathew, R., White, E.P., Thompson, C.B., Rabinowitz, J.D., 2013. Hypoxic and Ras-transformed cells support growth by scavenging unsaturated fatty acids from lysophospholipids. Proceedings of the National Academy of Sciences 110, 8882-8887.

Kim, C.-S., Kwon, Y., Choe, S.-Y., Hong, S.-M., Yoo, H., Goto, T., Kawada, T., Choi, H.-S., Joe, Y., Chung, H.T., 2015. Quercetin reduces obesity-induced hepatosteatosis by enhancing mitochondrial oxidative metabolism via heme oxygenase-1. Nutrition & metabolism 12, 1-9.

Kim, J.K., Park, S.U., 2018. Quercetin and its role in biological functions: an updated review. EXCLI journal 17, 856.

Kiwerska, K., Szyfter, K., 2019. DNA repair in cancer initiation, progression, and therapy—a double-edged sword. Journal of applied genetics 60, 329-334.

Kobori, M., Masumoto, S., Akimoto, Y., Oike, H., 2011. Chronic dietary intake of quercetin alleviates hepatic fat accumulation associated with consumption of a Western-style diet in C57/BL6J mice. Molecular nutrition & food research 55, 530-540.

Koundouros, N., Poulogiannis, G., 2020. Reprogramming of fatty acid metabolism in cancer. Br. J. Cancer 122, 4-22.

Kuhajda, F.P., 2000. Fatty-acid synthase and human cancer: new perspectives on its role in tumor biology. Nutrition 16, 202-208.

Lagunas-Rangel, F.A., Bermúdez-Cruz, R.M., 2020. Natural compounds that target DNA repair pathways and their therapeutic potential to counteract cancer cells. Frontiers in Oncology, 2567.

Langelier, M.-F., Eisemann, T., Riccio, A.A., Pascal, J.M., 2018. PARP family enzymes: regulation and catalysis of the poly (ADP-ribose) posttranslational modification. Curr. Opin. Struct. Biol. 53, 187-198.

Lee, S.-M., Moon, J., Cho, Y., Chung, J.H., Shin, M.-J., 2013. Quercetin up-regulates expressions of peroxisome proliferator-activated receptor γ, liver X receptor α, and ATP binding cassette transporter A1 genes and increases cholesterol efflux in human macrophage cell line. Nutrition Research 33, 136-143.

Leiherer, A., Stoemmer, K., Muendlein, A., Saely, C.H., Kinz, E., Brandtner, E.M., Fraunberger, P.,

Drexel, H., 2016. Quercetin impacts expression of metabolism-and obesity-associated genes in SGBS adipocytes. Nutrients 8, 282.

Li, J., Condello, S., Thomes-Pepin, J., Ma, X., Xia, Y., Hurley, T.D., Matei, D., Cheng, J.-X., 2017. Lipid desaturation is a metabolic marker and therapeutic target of ovarian cancer stem cells. Cell stem cell 20, 303-314. e305.

Lincet, H., Icard, P., 2015. How do glycolytic enzymes favour cancer cell proliferation by nonmetabolic functions? Oncogene 34, 3751-3759.

Lovejoy, C.A., Cortez, D., 2009. Common mechanisms of PIKK regulation. DNA repair 8, 1004-1008.

Ma, Q., Wang, J., Qi, J., Peng, D., Guan, B., Zhang, J., Li, Z., Zhang, H., Li, T., Shi, Y., 2021. Increased chromosomal instability characterizes metastatic renal cell carcinoma. Transl. Oncol. 14, 100929.

Mansoori, B., Mohammadi, A., Davudian, S., Shirjang, S., Baradaran, B., 2017. The different mechanisms of cancer drug resistance: a brief review. Advanced pharmaceutical bulletin 7, 339.

McNally, J.P., Millen, S.H., Chaturvedi, V., Lakes, N., Terrell, C.E., Elfers, E.E., Carroll, K.R., Hogan, S.P., Andreassen, P.R., Kanter, J., 2017. Manipulating DNA damage-response signaling for the treatment of immune-mediated diseases. Proceedings of the National Academy of Sciences 114, E4782-E4791.

Min, K., Ebeler, S.E., 2009. Quercetin inhibits hydrogen peroxide-induced DNA damage and enhances DNA repair in Caco-2 cells. Food and Chemical Toxicology 47, 2716-2722.

Mittelman, S.D., 2020. The role of diet in cancer prevention and chemotherapy efficacy. Annu. Rev. Nutr. 40, 273.

Moraes, M.C.S., Neto, J.B.C., Menck, C.F.M., 2012. DNA repair mechanisms protect our genome from carcinogenesis. Frontiers in Bioscience-Landmark 17, 1362-1388.

Murai, J., 2017. Targeting DNA repair and replication stress in the treatment of ovarian cancer. Int. J. Clin. Oncol. 22, 619-628.

Murai, J., Huang, S.-y.N., Das, B.B., Renaud, A., Zhang, Y., Doroshow, J.H., Ji, J., Takeda, S., Pommier, Y., 2012. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res. 72, 5588-5599.

Murakami, A., Ashida, H., Terao, J., 2008. Multitargeted cancer prevention by quercetin. Cancer letters 269, 315-325.

Murota, K., Shimizu, S., Chujo, H., Moon, J.-H., Terao, J., 2000. Efficiency of absorption and metabolic conversion of quercetin and its glucosides in human intestinal cell line Caco-2. Archives of Biochemistry and Biophysics 384, 391-397.

Muthukumaran, S., Sudheer, A.R., Menon, V.P., Nalini, N., 2008. Protective effect of quercetin on nicotine-induced prooxidant and antioxidant imbalance and DNA damage in Wistar rats. Toxicology 243, 207-215.

Nesic, K., Wakefield, M., Kondrashova, O., Scott, C.L., McNeish, I.A., 2018. Targeting DNA repair: the genome as a potential biomarker. The Journal of pathology 244, 586-597.

Nickoloff, J.A., Jones, D., Lee, S.-H., Williamson, E.A., Hromas, R., 2017. Drugging the cancers addicted to DNA repair. JNCI: Journal of the National Cancer Institute 109, djx059.

Oh, P.-J., Cho, J.-R., 2020. Changes in Fatigue, Psychological Distress, and Quality of Life After Chemotherapy in Women with Breast Cancer: A Prospective Study. Cancer Nurs. 43, E54-E60.

Okamoto, T., 2005. Safety of quercetin for clinical application. International journal of molecular medicine 16, 275-278.

Pisonero-Vaquero, S., Martínez-Ferreras, Á., García-Mediavilla, M.V., Martínez-Flórez, S., Fernández, A., Benet, M., Olcoz, J.L., Jover, R., González-Gallego, J., Sánchez-Campos, S., 2015. Quercetin ameliorates dysregulation of lipid metabolism genes via the PI3K/AKT pathway in a diet-induced mouse model of nonalcoholic fatty liver disease. Molecular Nutrition & Food Research 59, 879-893.

Ramos, A.A., Lima, C.F., Pereira, M., Fernandes-Ferreira, M., Pereira-Wilson, C., 2008. Antigenotoxic effects of quercetin, rutin and ursolic acid on HepG2 cells: evaluation by the comet assay. Toxicology Letters 177, 66-73.

Rather, R.A., Bhagat, M., 2020. Quercetin as an innovative therapeutic tool for cancer chemoprevention: Molecular mechanisms and

implications in human health. Cancer Medicine 9, 9181-9192.

Robey, R.W., Pluchino, K.M., Hall, M.D., Fojo, A.T., Bates, S.E., Gottesman, M.M., 2018. Revisiting the role of ABC transporters in multidrug-resistant cancer. Nature Reviews Cancer 18, 452-464.

Rysman, E., Brusselmans, K., Scheys, K., Timmermans, L., Derua, R., Munck, S., Van Veldhoven, P.P., Waltregny, D., Daniëls, V.W., Machiels, J., 2010. De novo lipogenesis protects cancer cells from free radicals and chemotherapeutics by promoting membrane lipid saturation. Cancer Res. 70, 8117-8126.

Salgia, R., Kulkarni, P., 2018. The genetic/non-genetic duality of drug 'resistance'in cancer. Trends in cancer 4, 110-118.

Scambia, G., Ranelletti, F., Panici, P.B., De Vincenzo, R., Bonanno, G., Ferrandina, G., Piantelli, M., Bussa, S., Rumi, C., Cianfriglia, M., 1994. Quercetin potentiates the effect of adriamycin in a multidrug-resistant MCF-7 human breast-cancer cell line: P-glycoprotein as a possible target. Cancer chemotherapy and pharmacology 34, 459-464.

Siegel, R.L., Miller, K.D., Fuchs, H.E., Jemal, A., 2021. Cancer statistics, 2021. CA Cancer J. Clin. 71, 7-33.

Snyder, A., Makarov, V., Merghoub, T., Yuan, J., Zaretsky, J.M., Desrichard, A., Walsh, L.A., Postow, M.A., Wong, P., Ho, T.S., 2014. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N. Engl. J. Med. 371, 2189-2199.

Soto-Heredero, G., Gomez de las Heras, M.M., Gabandé-Rodríguez, E., Oller, J., Mittelbrunn, M., 2020. Glycolysis–A key player in the inflammatory response. The FEBS journal 287, 3350-3369.

Sreedhar, A., Zhao, Y., 2018. Dysregulated metabolic enzymes and metabolic reprogramming in cancer cells. Biomedical reports 8, 3-10.

Stein, C.J., Colditz, G.A., 2004. Modifiable risk factors for cancer. Br. J. Cancer 90, 299-303.

Su, X., Abumrad, N.A., 2009. Cellular fatty acid uptake: a pathway under construction. Trends Endocrinol. Metab. 20, 72-77.

Torgovnick, A., Schumacher, B., 2015. DNA repair mechanisms in cancer development and therapy. Frontiers in genetics 6, 157.

Torre, L.A., Siegel, R.L., Ward, E.M., Jemal, A., 2016. Global Cancer Incidence and Mortality Rates and Trends—An UpdateGlobal Cancer Rates and Trends—An Update. Cancer Epidemiol. Biomarkers Prev. 25, 16-27.

Tosato, V., Grüning, N.-M., Breitenbach, M., Arnak, R., Ralser, M., Bruschi, C.V., 2013. Warburg effect and translocation-induced genomic instability: two yeast models for cancer cells. Front. Oncol. 2, 212.

Ulasova, E., Perez, J., Hill, B.G., Bradley, W.E., Garber, D.W., Landar, A., Barnes, S., Prasain, J., Parks, D.A., Dell'Italia, L.J., 2013. Quercetin prevents left ventricular hypertrophy in the Apo E knockout mouse. Redox Biology 1, 381-386.

Ündeğer, Ü., Aydın, S., Başaran, A.A., Başaran, N., 2004. The modulating effects of quercetin and rutin on the mitomycin C induced DNA damage. Toxicology letters 151, 143-149.

Vasan, N., Baselga, J., Hyman, D.M., 2019. A view on drug resistance in cancer. Nature 575, 299-309.

Wang, J., Lei, K., Han, F., 2018. Tumor microenvironment: recent advances in various cancer treatments. Eur. Rev. Med. Pharmacol. Sci. 22, 3855-3864.

Wang, Y., Yu, H., Wang, S., Gai, C., Cui, X., Xu, Z., Li, W., Zhang, W., 2021. Targeted delivery of quercetin by nanoparticles based on chitosan sensitizing paclitaxel-resistant lung cancer cells to paclitaxel. Materials Science and Engineering: C 119, 111442.

Warburg, O., 1956. On the origin of cancer cells. Science 123, 309-314.

Ward, R.A., Fawell, S., Floc'h, N., Flemington, V., McKerrecher, D., Smith, P.D., 2020. Challenges and opportunities in cancer drug resistance. Chem. Rev. 121, 3297-3351.

Wu, S., Zhu, W., Thompson, P., Hannun, Y.A., 2018. Evaluating intrinsic and non-intrinsic cancer risk factors. Nature Communications 9, 3490.

Xia, C., Dong, X., Li, H., Cao, M., Sun, D., He, S., Yang, F., Yan, X., Zhang, S., Li, N., 2022. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. Chin. Med. J. 135, 584-590.

Yi, H., Peng, H., Wu, X., Xu, X., Kuang, T., Zhang, J., Du, L., Fan, G., 2021. The therapeutic effects and mechanisms of quercetin on metabolic diseases: pharmacological data and clinical evidence. Oxidative medicine and cellular longevity 2021.

Yuan, R., Hou, Y., Sun, W., Yu, J., Liu, X., Niu, Y., Lu, J.J., Chen, X., 2017. Natural products to prevent drug resistance in cancer chemotherapy: a review. Ann. N. Y. Acad. Sci. 1401, 19-27.

Zhang, W., Zhang, S.-L., Hu, X., Tam, K.Y., 2015. Targeting tumor metabolism for cancer treatment: is pyruvate dehydrogenase kinases (PDKs) a viable anticancer target? Int. J. Biol. Sci. 11, 1390.

Zhao, Y., Butler, E.B., Tan, M., 2013. Targeting cellular metabolism to improve cancer therapeutics. Cell Death Dis. 4, e532-e532.