



Phytochemicals Modify the Action of Cancer Cells Mitochondrial Drug-Resistance Mechanism

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Abstract: The genesis and evolution of cancer are known to be significantly influenced by mitochondria, and recent studies have indicated that mitochondrial modifications may potentially contribute to the emergence of treatment resistance. Additionally, drug-resistant cancer cells may also display modifications in mitochondrial metabolism, such as changes in the generation of reactive oxygen species (ROS), which are biological byproducts of mitochondrial respiration. These changes can alter the cell's sensitivity to chemotherapy drugs and contribute to drug resistance. The expression of specific genes or proteins that are crucial in the control of cell growth and survival may be altered by mitochondrial mutations, which may also contribute to medication resistance. Phytochemicals are naturally occurring, biologically active substances found in plants that have been demonstrated to offer a variety of health advantages, including anti-cancer effects. It has been demonstrated that phytochemicals target these altered mitochondrial pathways in cancer cells, increasing the potency of chemotherapy medications and overcoming drug resistance. For instance, it has been demonstrated that some phytochemicals, including curcumin, resveratrol, and quercetin, can block the function of mitochondrial membrane proteins that lead to drug resistance in cancer cells. Other phytochemicals, including berberine and epigallocatechin gallate (EGCG), have been demonstrated to directly interfere with mitochondrial activity, inducing apoptosis (programmed cell death) in cancer cells. Overall, the capacity of phytochemicals to modify the functioning of cancer cell mitochondrial drug-resistance systems is a viable strategy for the creation of novel anti-cancer treatments.

Introduction

Mitochondrial energy metabolism is a complex process that occurs within the mitochondria, which are the powerhouses of the cell. Mitochondria are double-membraned organelles found in eukaryotic cells. The process of energy production within mitochondria involves several interconnected pathways, including the tricarboxylic acid (TCA) cycle, electron transport chain (ETC), and oxidative phosphorylation. The TCA cycle, also known as the citric acid cycle or Krebs cycle, takes place in the mitochondrial matrix (1). It involves a series of enzymatic reactions that oxidize acetyl-CoA, derived from the breakdown of carbohydrates, fatty acids, and amino acids, to produce energy-rich molecules such as NADH and FADH₂. These molecules carry high-energy electrons

that are further utilized in the ETC. The ETC is located in the inner mitochondrial membrane (2). It consists of a series of protein complexes, including NADH dehydrogenase, succinate dehydrogenase, cytochrome c reductase, and cytochrome c oxidase. These complexes facilitate the transfer of electrons from NADH and FADH₂ to molecular oxygen (O₂), generating a proton gradient across the inner mitochondrial membrane. The proton gradient established by the ETC drives ATP synthesis through a process called oxidative phosphorylation (3). ATP synthase, located in the inner mitochondrial membrane, utilizes the energy from the proton gradient to convert adenosine diphosphate (ADP) to ATP. This process is known as chemiosmosis and is critical for the efficient production of ATP. The oxidative phosphorylation process used by mitochondria to

produce energy is essential for cellular metabolism. They are also involved in controlling reactive oxygen species (ROS) and other cellular processes including apoptosis and calcium homeostasis. Reactive oxygen species (ROS) are important regulators of apoptosis, a tightly regulated process of programmed cell death, in normal physiological settings. Superoxide anion (O₂⁻), hydrogen peroxide (H₂O₂), and hydroxyl radical (OH⁻) are examples of naturally occurring reactive oxygen species (ROS) that are involved in a number of biological communication pathways. Calcium signals are strictly controlled under normal circumstances to ensure proper cellular responses. The activation of several enzymes, transcription factors, and other signaling molecules is mediated by calcium ions, which function as second messengers. They play a role in the control of actions such as cell division, differentiation, apoptosis, and the release of neurotransmitters. Cancer formation and progression have both been linked to mitochondrial malfunction, and as the disease progresses, mitochondria undergo a number of changes (4).

One of the significant modifications observed during cancer is the alteration of the mitochondrial DNA (mtDNA). MtDNA is a circular genome that codes for several critical proteins involved in oxidative phosphorylation. Studies have revealed that mtDNA mutations occur in a number of cancer forms, including breast, lung, and prostate cancer. These mutations can result in the creation of aberrant proteins, which can affect mitochondrial function and result in modifications to cellular metabolism and signaling pathways (5). The alteration in mitochondrial shape is another mitochondrial modification seen during malignancy. Maintaining mitochondrial homeostasis and function requires mitochondrial fusion and fission. The equilibrium between mitochondrial fusion and fission is upset in cancer cells, changing the shape of the mitochondria. These modifications may influence signaling pathways as well as how mitochondria interact with other cellular organelles like the endoplasmic reticulum (5). Changes in mitochondrial metabolism also occur during cancer progression. The Warburg effect, which occurs even when oxygen levels are normal, describes how glycolysis plays a significant role in the energy generation of cancer cells. This change in metabolism is assumed to be brought on by modifications in mitochondrial activity, including a reduction in oxidative phosphorylation and an increase in ROS generation. Additionally, cancer cells can upregulate alternative metabolic pathways such as glutaminolysis, which can further alter mitochondrial metabolism (6).

Mitochondrial modifications can also impact the apoptotic pathway, a process that regulates cell death. Fission and fusion imbalances can impair mitochondrial function and cause cell death. Defective fusion, on the

other hand, can result in mitochondrial malfunction and necrotic cell death, whilst excessive fission has been linked to apoptosis. In cancer cells, the apoptotic pathway is often altered, allowing cells to avoid programmed cell death. By modifying the expression of pro- and anti-apoptotic proteins and affecting the mitochondrial membrane potential, which is essential for the release of apoptotic agents, mitochondrial changes can have an influence on the apoptotic pathway (7). Drug resistance in cancer cells can be brought on by mutations in mtDNA and modifications to the electron transport chain (ETC). Changes in mitochondrial membrane potential, the opening of the mitochondrial permeability transition pore (mPTP), and ATP production are all components of mitochondrial drug resistance (MDR), which can alter drug absorption and efflux as well as the apoptotic signaling pathway (8). Upregulation of ATP-binding cassette (ABC) transporters on the mitochondrial outer membrane, which may pump medicines out of cells, is one of the main mechanisms of MDR. The efflux of chemotherapeutic drugs is facilitated by ABC transporters, including breast cancer resistance protein (BCRP), multidrug resistance-associated protein (MRP), and P-glycoprotein (P-gp) which are overexpressed in various types of cancer cells. This reduces drug accumulation in the cells. Cancer patients' poor clinical outcomes and worse survival rates are frequently linked to the overexpression of these transporters (9). The modification of the mitochondrial membrane potential ($\Delta\psi_m$), which is necessary for the correct operation of the ETC and ATP production, is another mechanism of MDR. The ATP synthase complex and the electron transport chain are active, creating a proton gradient across the inner mitochondrial membrane, which is necessary for the maintenance of $\Delta\psi_m$. Drug transporter expression and function are changed in cancer cells, resulting in decreased drug absorption and increased efflux (10).

The MDR process also involves the opening of the mPTP. The mitochondrial permeability, apoptosis, and necrosis are regulated by the non-selective mPTP channel, which crosses the inner and outer mitochondrial membranes. Apoptosis can occur as a result of the mPTP being opened because it can cause the release of cytochrome c and other pro-apoptotic components from the mitochondria. However, cancer cells with altered mPTP activity can evade apoptosis and exhibit MDR (8). Along with these processes, MDR can also be brought on by modifications in mitochondrial metabolism, such as those in glycolysis, oxidative phosphorylation, and fatty acid metabolism. These modifications can modify the apoptotic signaling pathway and have an impact on medication efflux and absorption. Recent research has emphasized the significance of MDR and mitochondrial metabolism targeting in cancer treatment. In preclinical and clinical

trials, novel medicines and treatment methods that target mitochondrial function, such as mPTP inhibitors, ETC complex inhibitors, and modulators of mitochondrial metabolism, have demonstrated encouraging outcomes (11). Recent studies have demonstrated that several phytochemicals, such as curcumin, resveratrol, and quercetin, can modify the function of the mitochondrial drug-resistance mechanism in cancer cells, increasing the susceptibility to chemotherapeutic medicines. For instance, it has been demonstrated that curcumin causes apoptosis in cancer cells by changing the potential of the mitochondrial membrane and boosting the production of reactive oxygen species (ROS). Similar to this, it has been demonstrated that resveratrol causes changes in mitochondrial activity and lowers ATP generation in

cancer cells, increasing apoptosis (12-13). By blocking the activity of certain enzymes involved in the metabolism of chemotherapeutic medicines, phytochemicals may also change the mitochondrial drug-resistance mechanism in cancer cells. For instance, it has been demonstrated that quercetin reduces the activity of cytochrome P450 enzymes, which are crucial for the metabolism of certain chemotherapeutic medicines (14). In conclusion, the capacity of phytochemicals (flavonoids, terpenoids and polyphenols) to modify the functioning of the mitochondrial drug-resistance mechanism in cancer cells is an area of current research and holds promise for the creation of innovative anti-cancer medicines. To completely comprehend the underlying processes and to determine the best chemicals and doses for therapeutic usage, more research is required.

Table 1. Different types of mitochondrial structural and functional changes modulate drug-resistance.

Structural and Functional Changes	Cancer Type	Drug Resistance	Ref.
Increased mitochondrial biogenesis	Breast cancer	Tamoxifen resistance	(42)
Altered mitochondrial morphology	Ovarian cancer	Platinum resistance	(43)
Elevated mitochondrial membrane potential	Lung cancer	EGFR-TKI resistance	(44)
Upregulated oxidative phosphorylation	Prostate cancer	Enzalutamide resistance	(45)
Reduced mitochondrial DNA content	Colon cancer	5-FU resistance	(46)
Enhanced mitochondrial fission	Leukemia	TKI resistance	(47)
Impaired mitochondrial respiration	Melanoma	BRAF inhibitor resistance	(48)
Decreased mitochondrial calcium uptake	Pancreatic cancer	Gemcitabine resistance	(49)
Elevated mitochondrial ROS production	Renal cell carcinoma	Trastuzumab resistance	(50)
Reduced mitochondrial protein synthesis	Gastric cancer	Sunitinib resistance	(51)

Mitochondrial Structural and Functional Changes Modulating Drug-resistance

Here, we discuss the structural and number changes in mitochondria observed during cancer (see Table 1). The heart of eukaryotic cells, mitochondria are in charge of generating ATP, the main source of cellular energy. Additionally, they are essential for several cellular activities like signaling, apoptosis, and metabolism. A growing body of research indicates that mitochondria are crucial to the initiation and development of cancer (5). Mitochondrial fragmentation, in which the organelles are smaller and more numerous, is one of the most persistent structural alterations seen in cancer cells. Mitochondrial fragmentation is often accompanied by a decrease in cristae density, which is the site of oxidative phosphorylation. In contrast, normal mitochondria have a highly organized and interconnected structure, with densely packed cristae. The imbalance between fission and fusion is disturbed, leading to the production of smaller mitochondria, which is related with altered mitochondrial dynamics

and the fragmented mitochondria in cancer cells (15). It is believed that abnormalities in mitochondrial number are connected to the changes in mitochondrial structure seen in cancer cells. Cancer cells often exhibit an increased number of mitochondria, which can be attributed to increased mitochondrial biogenesis or decreased mitophagy, a process where damaged mitochondria are selectively degraded. Increased mitochondrial biogenesis has been linked to the emergence of chemotherapy resistance in various cancer types, including prostate cancer (16). Several studies have identified the molecular mechanisms underlying the changes in mitochondrial structure and number in cancer. For instance, changes in the expression or activity of proteins involved in mitochondrial fission and fusion, such as dynamin-related protein 1 (Drp1), mitofusin 1 and 2 (Mfn1 and Mfn2), and optic atrophy 1 (OPA1), have been linked to changes in mitochondrial dynamics. The expression or activity of transcription factors and regulatory proteins, such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1) and PTEN-induced putative kinase 1 (PINK1), is frequently altered in response to changes in mitochondrial biogenesis and mitophagy (17). In summary, cancer cells exhibit

significant changes in mitochondrial structure and number, including mitochondrial fragmentation, decreased cristae density, increased mitochondrial number, and alterations in mitochondrial dynamics. Changes in the expression and activity of proteins involved in mitochondrial fission and fusion, biogenesis, and mitophagy are linked to these changes. For the creation of efficient cancer therapeutics, it is essential to comprehend the processes driving these alterations in mitochondrial function and quantity.

In cancer cells, mitochondrial ROS (reactive oxygen species) play a critical role in treatment resistance. ROS are a consequence of cellular respiration and are essential for redox equilibrium and cell signaling. However, excessive ROS can result in oxidative damage to proteins, lipids, and other cellular constituents including DNA, which can kill cells. Cancer cells have evolved mechanisms to adapt to high ROS levels, which contributes to drug resistance. The mitochondrial electron transport chain (ETC) is one of the methods through which cancer cells control the amounts of reactive oxygen species (ROS). The ETC is a collection of proteins and enzymes that produce ATP (adenosine triphosphate) by oxidative phosphorylation in the mitochondrial membrane. During this process, electrons from the ETC escape and interact with oxygen to produce ROS. Cancer cells can upregulate the ETC to generate more ATP, which, in turn, increases ROS levels. High ROS levels can activate a number of signaling pathways that support cell survival and drug resistance, including PI3K/Akt, MAPK/ERK, and NF- κ B (18). A number of studies have demonstrated that blocking the ETC can make cancer cells more susceptible to chemotherapy and overcome drug resistance. For instance, metformin, a medication for type 2 diabetes, has the ability to block mitochondrial complex I, which results in decreased ATP generation and increased ROS levels, making cancer cells more susceptible to chemotherapy (19). Inhibiting mitochondrial complex III with the medication atovaquone has been shown to make cancer cells more susceptible to chemotherapy and overcome drug resistance (20).

The mitochondria of eukaryotic cells contain mitochondrial DNA (mtDNA), a circular double-stranded DNA molecule. It produces ATP by the oxidative phosphorylation of 13 proteins, 22 transfer RNAs (tRNAs), and 2 ribosomal RNAs (rRNAs) that it encodes. Recent studies suggest that mtDNA mutations and alterations can regulate drug-resistance in cancer cells (21). Drug resistance is a significant barrier to treating cancer and is linked to poor therapeutic results. Several processes, including overexpression of efflux transporters, activation of survival pathways, and mutation of drug targets, can lead to drug resistance in cancer cells. But according to current research, mtDNA

changes can also be vital in controlling cancer cells' treatment resistance (22). One of the mechanisms by which mtDNA alterations regulate drug-resistance is through the modulation of oxidative phosphorylation and energy metabolism. Cancer cells with mtDNA mutations often have altered oxidative phosphorylation and energy metabolism, which can contribute to drug-resistance. For example, cancer cells with mtDNA mutations may have increased aerobic glycolysis and decreased oxidative phosphorylation, which can confer resistance to drugs that target oxidative phosphorylation, such as metformin (23). Reactive oxygen species (ROS) levels can be altered, which is another way that mtDNA changes might control medication resistance. ROS are very reactive chemicals that may harm DNA, proteins, and lipids. They are also essential for the development of cancer and the development of treatment resistance. ROS levels in cancer cells with mtDNA mutations are frequently changed, and this can result in treatment resistance. For instance, ROS levels may be lower in cancer cells with mtDNA mutations, which may confer resistance to medications that cause ROS-mediated cell death, such as cisplatin (24). Certain mtDNA mutations and changes have been linked to treatment resistance in cancer cells, according to recent research. For instance, it has been demonstrated that the mtDNA mutation m.3243A>G confers cisplatin resistance in ovarian cancer cells through modifying ROS levels. It has been demonstrated that the mtDNA deletion m.4977 alters energy metabolism in breast cancer cells to provide resistance to doxorubicin. According to these findings, focusing on mtDNA mutations may be a potential way to combat cancer medication resistance (25).

The metabolism of glutamine in the mitochondria is essential for cancer drug resistance. Glutamine is a crucial nutrition for cancer cells because it offers crucial substrates for biosynthesis, energy generation, and antioxidant defenses. Mitochondrial glutamine metabolism, specifically the glutamine-dependent reductive carboxylation pathway, provides an important anaplerotic source of citrate for fatty acid synthesis, and NADPH for antioxidant defense. It has been demonstrated that blocking this route can overcome drug resistance in cancer cells and make them more sensitive to different types of chemotherapy and immunotherapy. It's critical to remember that depending on the kind of cancer and genetic changes present in the tumor, different paths and treatments can be used to overcome medication resistance. Therefore, a customized strategy taking into account each patient's tumor's molecular profile is essential for determining the most efficient techniques (26). Recent research has revealed a new medicine called CB-839 that works by inhibiting the glutamine-dependent reductive carboxylation pathway by

targeting glutaminase, the enzyme that catalyzes the conversion of glutamine to glutamate. The enzyme glutamine synthetase (GS), which catalyzes the conversion of glutamate and ammonia into glutamine, is essential for nitrogen metabolism. The appropriate nitrogen balance in cells is maintained by closely controlling the activity of the highly regulated enzyme GS. The capacity of GS to directly absorb ammonia into glutamate, even at low ammonia concentrations, is one of its standout characteristics. Scavenging ammonia and avoiding its harmful accumulation in cells are essential goals of this mechanism. In preclinical cancer models, CB-839 has been demonstrated to increase the effectiveness of a number of chemotherapy drugs, such as gemcitabine, cisplatin, and paclitaxel. It is now being tested in human studies with chemotherapeutic drugs for a variety of cancer types. AOA (aminooxyacetate), a different medication, has also been demonstrated to suppress glutaminase activity and make cancer cells more susceptible to chemotherapy (27). In preclinical models of a number of cancer types, including lung cancer, breast cancer, and ovarian cancer, it has been demonstrated that AOA, a small molecule inhibitor that covalently binds to the active site of glutaminase, has powerful antitumor effects (28). Recent research has also shown additional targets in mitochondrial glutamine metabolism that might be used to combat cancer medication resistance in addition to glutaminase inhibitors. For instance, the transport of pyruvate into the mitochondrial matrix for oxidative phosphorylation and citrate production is crucially regulated by the mitochondrial pyruvate carrier (MPC). It has been demonstrated that MPC inhibition lowers mitochondrial respiration and increases cancer cells' susceptibility to chemotherapy (29-30). The TCA cycle is a crucial metabolic system that uses a number of enzyme-catalyzed events to change pyruvate into ATP, NADH, and FADH₂. The TCA cycle is upregulated in cancer cells, which results in enhanced ATP generation and treatment resistance. Recent research has demonstrated that through controlling mitochondrial respiration and oxidative stress, the TCA cycle enzyme fumarate hydratase (FH) can decrease tumor growth in renal cell carcinoma (RCC) (31). Isocitrate dehydrogenase (IDH), a TCA cycle enzyme, has also been linked to the emergence of glioblastoma, with mutations in IDH1/2 resulting in elevated TCA cycle activity and carcinogenesis (32). The inner mitochondrial membrane contains a group of electron carriers called the ETC, which provide a proton gradient that propels the production of ATP. The ETC is frequently overexpressed in cancer cells, which results in enhanced energy generation and treatment resistance. Targeting ETC complex I has been found to make cancer cells more susceptible to chemotherapy (33). Furthermore, it has been demonstrated that the ETC complex III functions as a mediator of oxidative stress and treatment resistance in breast cancer (34).

A class of transmembrane transporters known as mitochondrial ATP-binding cassette subfamily B (ABCB) proteins is essential for controlling drug resistance in cancer cells. These proteins have a role in the active efflux of chemotherapeutic medications from cancer cells, which can result in a reduction in drug accumulation and a reduction in therapeutic effectiveness. Among the mitochondrial ABCB proteins, ABCB6 has been identified as the only mitochondrial ABCB protein that regulates drug resistance in cancer (35). Cancer cells that are resistant to treatment produce large levels of the mitochondrial transporter ABCB6. It has been demonstrated to be essential for the efflux from the mitochondria of cancer cells of chemotherapeutic drugs such as mitoxantrone, doxorubicin, and daunorubicin. It has been demonstrated that inhibiting ABCB6 expression or activity increases the accumulation of these medicines in cancer cells, improving therapeutic effectiveness (36). Several studies have demonstrated the clinical relevance of ABCB6 in drug-resistant cancer. For instance, research by Huang and colleagues discovered that drug-resistant ovarian cancer cells expressed ABCB6 substantially more than drug-sensitive cells, and that knocking down ABCB6 expression made these cells more responsive to chemotherapeutic drugs. Similarly, ABCB6 expression was linked to a poor prognosis in individuals with stomach cancer, according to research by Zhang and colleagues, and ABCB6 inhibition enhanced the susceptibility of gastric cancer cells to chemotherapeutic drugs (37). Recent studies have also identified potential strategies for targeting ABCB6 in drug-resistant cancer. For example, a study by Lu and colleagues found that inhibition of ABCB6 expression using siRNA nanoparticles sensitized drug-resistant breast cancer cells to chemotherapeutic agents. Similar findings were made in research by Zhang and colleagues, who discovered that the small molecule inhibitor RMM-46 has the ability to block ABCB6 activity and make chemotherapy-resistant cancer cells susceptible (38).

The mitochondrial DNA (mtDNA) repair pathway is one of the most researched mechanisms behind mitochondrial resistance to drugs in cancer. The mtDNA repair pathway is responsible for repairing the damage caused by chemotherapy drugs to mtDNA. Cancer cells that develop resistance to chemotherapy drugs can upregulate the mtDNA repair pathway, which allows them to repair the mtDNA damage caused by the drugs and survive. The activation of the mitochondrial unfolded protein response (UPR_{mt}) pathway, which controls the expression of mtDNA repair genes, or mutations in the mtDNA repair genes OGG1 and MUTYH can both result in this increase (39). The mitochondrial membrane potential (MMP) route is another mechanism connected to mitochondrial drug resistance in cancer. The ATP generation process and

cell viability depend on the electrochemical gradient that the MMP route controls across the mitochondrial inner membrane. Chemotherapy drugs can disrupt the MMP, leading to mitochondrial dysfunction and cell death. Cancer cells that develop resistance to chemotherapy drugs can upregulate the MMP pathway, which allows them to maintain the electrochemical gradient and survive. The activation of the mitochondrial permeability transition pore (mPTP), which controls the MMP, or the induction of anti-apoptotic Bcl-2 family members, which block mPTP opening, can both result in this increase (40). Last but not least, the mitochondrial biogenesis pathway has also been connected to cancer treatment resistance in mitochondria. The process through which new

mitochondria are created in response to cellular energy requirements is known as mitochondrial biogenesis. Cancer cells that develop resistance to chemotherapy drugs can upregulate the mitochondrial biogenesis pathway, which allows them to increase their mitochondrial mass and survive. The PGC-1 α pathway, which controls mitochondrial biogenesis, can be stimulated in order to cause this increase (41). In conclusion, complicated interactions across several pathways, such as mtDNA repair, MMP control, and mitochondrial biogenesis, are involved in the molecular processes of mitochondrial drug resistance in cancer. Understanding these pathways and how they are controlled may help researchers create fresh approaches to combat mitochondrial drug resistance in cancer.

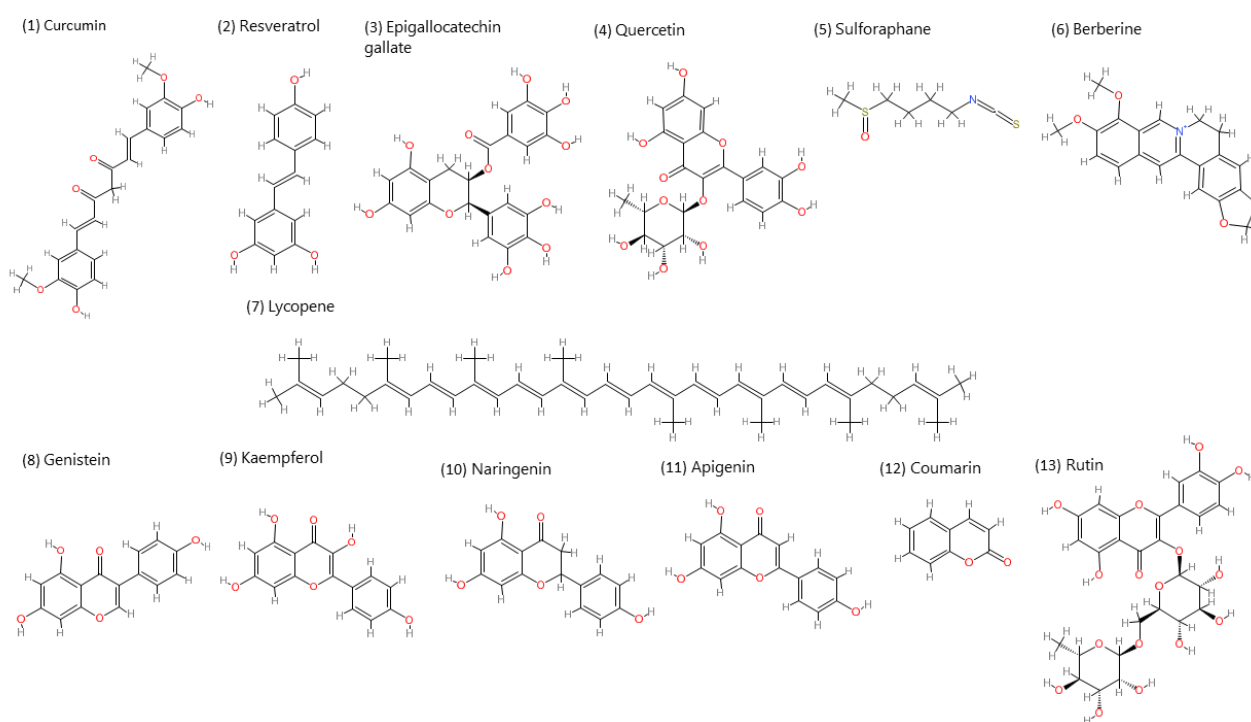


Figure 1. Phytochemicals preventing the mitochondrial drug-resistance mechanism.

Alternative Therapy for Mitochondrial Drug-resistance: Phytochemicals

Biologically active substances called phytochemicals are present in plants and are thought to provide health advantages, including anticancer characteristics (see Figure 1). Growing evidence points to a potential function for phytochemicals in the management and treatment of cancer (52). The flavonoids are one of the phytochemical classes that has been the subject of the most research. A sizable collection of polyphenolic substances known as flavonoids may be found in fruits, vegetables, and other plant-based meals. They are known to have anti-inflammatory, antioxidant, and

anti-cancer characteristics, and multiple studies have found a decreased risk of cancer in those who consume a lot of flavonoids in their diets (53). The potential health advantages of these substances, notably their anticancer qualities, have drawn a lot of interest. Numerous pathways exist in flavonoids that support their anticancer properties. Antioxidant action, cellular signaling pathway modification, anti-inflammatory effects, cell cycle arrest induction, promotion of apoptosis (planned cell death), and suppression of angiogenesis (the creation of new blood vessels to promote tumor growth) are a few of these methods (54). All of these actions contribute to reducing the risk of cancer development, spread, and metastasis. Inhibiting the activity of matrix metalloproteinases (MMPs) and regulating the generation of reactive

oxygen species (ROS) are two ways flavonoids exercise their anticancer effects. Because flavonoids have antioxidant characteristics, they can scavenge free radicals and reactive oxygen species (ROS), which can damage DNA and encourage the growth of cancer (55). Flavonoids assist in protecting cells from genetic alterations and halting the start of carcinogenesis by lowering oxidative stress. Flavonoids, for instance, can control the production of anti-apoptotic proteins like Bcl-2 and Bcl-xL. These proteins work to preserve the

potential of the mitochondrial membrane by preventing the release of cytochrome c and the consequent activation of apoptotic pathways (56). Reactive oxygen species (ROS) produced during mitochondrial respiration can be scavenged by flavonoids since they also have antioxidant capabilities. The loss of mitochondrial membrane potential ($\Delta\Psi_m$) and dysfunctional mitochondria can result from excessive ROS generation. By lowering ROS levels, flavonoids can support maintaining m and preserving mitochondrial function (57).

Table 2. Different types of phytochemicals used as an alternative therapy for mitochondrial drug-resistance.

Phytochemical	Cancer Type	Mitochondrial Target	Effect	Ref.
Curcumin	Breast	Complex I	Inhibits ATP production, triggers apoptosis	(114)
Resveratrol	Leukemia	Complex III	Increases ROS production, induces cell death	(115)
Epigallocatechin gallate (EGCG)	Prostate	Complex I	Inhibits ATP production, activates caspases	(116)
Quercetin	Colon	Complex III	Decreases ATP production, increases ROS production, induces apoptosis	(117)
Sulforaphane	Lung	Complex I	Decreases ATP production, activates caspases	(118)
Berberine	Liver	Complex I	Inhibits ATP production, induces mitochondrial membrane depolarization	(119)
Lycopene	Pancreas	Complex III	Inhibits ATP production, triggers apoptosis	(120)
Genistein	Bladder	Complex II	Inhibits ATP production, induces mitochondrial membrane depolarization	(121)
Kaempferol	Skin	Complex III	Increases ROS production, triggers apoptosis	(122)
Naringenin	Ovarian	Complex I	Inhibits ATP production, induces mitochondrial membrane depolarization	(123)
Apigenin	Breast	Complex II	Inhibits ATP production, induces mitochondrial membrane depolarization	(124)
Coumarin	Ovarian	Complex I	Inhibits ATP production, induces mitochondrial membrane depolarization	(109)
Rutin	Glioblastoma	Complex IV	Inhibits ATP production, triggers apoptosis	(112)

The carotenoids are a different class of phytochemicals that have undergone substantial research for their possible anticancer effects. The group of plant pigments known as carotenoids is what gives fruits and vegetables their yellow, orange, and red hues. Numerous studies have shown that those who consume large amounts of carotenoids, notably the tomato-derived lycopene, have a decreased chance of developing cancer. Resveratrol, which is present in red wine and grapes, as well as curcumin, which is present in turmeric, are other phytochemicals that have been investigated for their potential anticancer activities (51). Although the evidence supporting phytochemicals' anticancer abilities is still developing, numerous studies have shown encouraging findings. For instance, research indicated that women who consumed more flavonoids had a decreased risk of breast cancer than those who consumed less, according to a publication in the journal *Cancer Epidemiology, Biomarkers & Prevention*. Men who

consumed a lot of lycopene had a decreased chance of developing prostate cancer, according to another research (52) that was printed in the *Journal of the National Cancer Institute*. Overall, the data point to a potential role for phytochemicals in the prevention and management of cancer. To completely comprehend the processes behind their anticancer activities and to establish the ideal phytochemical dosages and sources for cancer prevention and therapy, additional study is nonetheless required.

Drug resistance is a multifactorial phenomenon that can develop in tumor cells as a result of several genetic and epigenetic alterations. Researchers are looking at novel approaches to combat drug resistance in cancer, one of which is the use of phytochemicals. Plants include physiologically active substances called phytochemicals, which have been demonstrated to have anti-cancer potential (53). Due to their ability to make chemotherapy-resistant cancer cells more

susceptible, phytochemicals have attracted a lot of attention in the field of cancer research. The many and intricate processes by which phytochemicals exercise their anti-cancer actions include the control of several signaling pathways, the activation of apoptosis, the modification of cell cycle progression, and the suppression of angiogenesis. Additionally, phytochemicals have been demonstrated to increase the effectiveness of chemotherapy medications, enhancing cancer patients' overall response rates and chances of survival (58). Numerous phytochemicals have the ability to combat cancer medication resistance, according to recent studies. For instance, curcumin, a naturally occurring substance present in turmeric, has been demonstrated to sensitize chemotherapy-resistant cancer cells by reducing the function of transporters that promote multidrug resistance. Similar to this, it has been demonstrated that the polyphenol resveratrol, which is present in grapes and red wine, increases the susceptibility of cancer cells to chemotherapy by suppressing the expression of drug resistance genes (59). Sulforaphane, another potential phytochemical, is present in cruciferous vegetables like broccoli and cauliflower. Sulforaphane has been demonstrated to induce apoptosis and suppress the production of drug resistance genes in cancer cells, making them more susceptible to chemotherapy. The polyphenol epigallocatechin gallate (EGCG), which is present in green tea, has also been demonstrated to improve the effectiveness of chemotherapy treatments in cancer cells that are resistant to treatment (60). In conclusion, phytochemicals provide a viable strategy to combat cancer medication resistance. A novel treatment option for cancer is made possible by phytochemicals' capacity to make chemotherapy more effective and to make drug-resistant cancer cells more susceptible to it (see Table 2). To completely comprehend how phytochemicals work and their potential as cancer treatments, more study is required.

Curcumin

Curcumin, a naturally occurring polyphenol produced from turmeric, has been demonstrated to possess strong anticancer capabilities by obstructing key cellular processes involved in the development of cancer. According to recent research, curcumin also inhibits the mitochondrial drug-resistance pathways found in cancer cells (61). The heart of the cell, mitochondria are essential for both the pathways leading to cell death and the metabolism of energy. Drug resistance in cancer cells has been related to mitochondrial malfunction. The altered mitochondrial membrane potential of resistant to drugs cancer cells affects the effectiveness of anticancer medications that target mitochondrial pathways. It has been demonstrated that curcumin targets the mitochondrial mechanisms responsible for cancer cells' treatment

resistance. The modulation of the expression of Bcl-2 family proteins is one of the ways that curcumin works. A family of proteins known as Bcl-2 family members controls the mitochondrial mechanism of apoptosis. It has been demonstrated that curcumin increases the expression of pro-apoptotic Bax proteins while decreasing the expression of anti-apoptotic Bcl-2 proteins. As a result, the mitochondrial membrane becomes more permeable, which causes cancer cells to undergo apoptosis (62). According to reports, curcumin also affects the mitochondrial electron transport chain (ETC), which is in charge of producing ATP and reactive oxygen species (ROS). The ETC is frequently hyperactive in drug-resistant cancer cells, which increases ROS generation and causes oxidative stress. According to research, curcumin reduces the activity of the ETC complex I, which lowers the creation of ROS and oxidative stress in cancer cells. As a result, cancer cells' drug resistance is reversed and their mitochondrial function is restored (63). The AMP-activated protein kinase (AMPK) pathway, a crucial regulator of cellular energy metabolism, has also been demonstrated to be a target of curcumin. The AMPK pathway is frequently dysregulated in cancer cells with enhanced treatment resistance, altering their metabolic profile. It has been demonstrated that curcumin activates the AMPK system, reversing drug resistance in cancer cells and restoring normal cellular energy metabolism (64). As a result of its ability to target the mitochondrial pathways responsible for cancer cells' development of drug resistance, curcumin possesses strong anticancer effects. It is a promising candidate for the creation of brand-new anticancer treatments because of its capacity to control the expression of Bcl-2 family members, limit the activity of the ETC, and activate the AMPK pathway.

Resveratrol

A naturally occurring polyphenol called resveratrol is present in many plants, including berries, grapes, and peanuts. Its potential for health benefits, especially its anticancer effects, have been well researched. The maintenance of cellular homeostasis depends heavily on mitochondria, and medication resistance in cancer cells has been associated with mitochondrial malfunction. It has been demonstrated that resveratrol targets the cancer cells' mitochondrial drug resistance pathway to provide its anticancer effects. Multidrug resistance-associated protein (MRP) and P-glycoprotein (P-gp), two proteins involved in the efflux of medicines from cancer cells, are upregulated as part of the mitochondrial drug-resistance mechanism. The production and activity of these proteins have been demonstrated to be inhibited by resveratrol, which increases the susceptibility of cancer cells to chemotherapy treatments (65). Resveratrol also affects the signaling pathways that control cell proliferation, death, and angiogenesis in order to exercise its

anticancer effects. Inhibiting mTOR signaling, a mechanism that encourages cell growth and proliferation, stimulates the AMP-activated protein kinase (AMPK) pathway, which controls cellular energy balance. By activating the caspase cascade, upregulating pro-apoptotic proteins like Bax and downregulating anti-apoptotic proteins like Bcl-2, resveratrol also causes apoptosis in cancer cells (66). The transcription factor nuclear factor-kappaB (NF- κ B), which controls inflammation and cell viability, has also been found to be inhibited by resveratrol. In cancer cells, NF- κ B is frequently overactivated, which aids in the survival and growth of these cells. By preventing NF- κ B's nuclear translocation and stifling the activity of IKK, an upstream kinase that activates NF- κ B, resveratrol reduces NF- κ B activity (67). Additionally, recent research has looked at how resveratrol affects the gut flora and how that may affect cancer therapy and prevention. Resveratrol has been demonstrated to alter the gut microbiota's makeup and activity, which can affect the host immune system and alter how the body reacts to cancer treatments (68). As a result, resveratrol targets the mitochondrial drug-resistance mechanism, modifies multiple signaling pathways that control cell growth and death, and modifies the gut microbiota to exercise its anticancer effects. To completely understand resveratrol's methods of action and its potential as a cancer treatment, more research is required.

Epigallocatechin Gallate (EGCG)

A significant challenge in the treatment of cancer is mitochondrial medication resistance. The upregulation of multidrug resistance proteins (MRPs) on the mitochondrial membrane, which promotes drug efflux from the mitochondria, is one of the hypothesized mechanisms of mitochondrial drug resistance. Green tea catechin EGCG, which inhibits MRPs and restores drug accumulation in the mitochondria, has been proven to make cancer cells more susceptible to chemotherapeutic treatments. By interacting with the ATP-binding sites in MRPs, EGCG has been demonstrated to limit their activity. MRPs are ATP-dependent drug efflux pumps that move medications out of mitochondria and cells. The activity of a number of MRPs, including MRP1, MRP2, and MRP3, has been found to be inhibited by EGCG in cancer cells (69). Because EGCG inhibits MRPs, more medicines accumulate in mitochondria, which increases the risk of mitochondrial damage and death in cancer cells. EGCG has been demonstrated to alter a number of additional signaling pathways associated with mitochondrial drug resistance in addition to blocking MRPs. In cancer cells, EGCG has been shown to upregulate the expression of pro-apoptotic proteins like Bax and Bak while downregulating the expression of anti-apoptotic proteins like Bcl-2 and Bcl-xL (70). As a result, the mitochondrial outer membrane becomes more

permeable (MOMP) and releases cytochrome c, which in turn triggers the caspase cascade and causes death in cancer cells. The AMP-activated protein kinase (AMPK) pathway, which is important in energy metabolism and cellular stress response, has also been discovered to be activated by EGCG (71). Inhibition of mTOR signaling and activation of autophagy are caused by EGCG's activation of AMPK in cancer cells, which can facilitate the destruction of damaged mitochondria and improve mitochondrial quality control. This might help EGCG sensitize cancer cells to chemotherapeutic medicines. In conclusion, EGCG sensitizes cancer cells to chemotherapy drugs by inhibiting MRPs, modulating apoptotic pathways, and activating the AMPK pathway. These mechanisms contribute to the restoration of drug accumulation in the mitochondria and enhanced mitochondrial damage and apoptosis in cancer cells. EGCG has shown promising results in preclinical studies as a sensitizer to chemotherapy drugs in cancer treatment, and further clinical studies are warranted.

Quercetin

Natural flavonoid quercetin has been thoroughly investigated for its potential to reduce the development and proliferation of cancer cells. One of the ways quercetin exerts its anti-cancer effects is through its ability to overcome mitochondrial drug resistance mechanisms that contribute to chemoresistance in cancer cells (72). Cancer cells can develop a resistance to chemotherapy treatments known as mitochondrial drug resistance by upregulating the production of anti-apoptotic proteins and changing mitochondrial function. These alterations provide cancer cells a way to avoid the cell death brought on by chemotherapy medications, which eventually results in treatment failure. It has been demonstrated that quercetin reduces drug resistance in mitochondria by modifying mitochondrial activity and preventing the production of proteins that prevent apoptosis (73). One way quercetin modifies mitochondrial function is by preventing complex I in the electron transport chain (ETC) from doing its job. The essential element of the ETC that produces ATP, the cellular energy unit, is Complex I. Quercetin decreases ATP synthesis by blocking complex I activity, which results in a drop in the mitochondrial membrane potential (m) and an increase in the formation of ROS in the mitochondria. Since mitochondrial malfunction and oxidative stress are two major factors that contribute to apoptosis, these modifications eventually cause an increase in apoptosis in cancer cells (74). The anti-apoptotic proteins Bcl-2 and Bcl-xL, which are overexpressed in cancer cells and increase treatment resistance by blocking the intrinsic apoptotic pathway, are likewise inhibited by quercetin. Quercetin promotes apoptosis in cancer cells and makes them more susceptible to chemotherapy treatments by decreasing

the production of these proteins (75). Quercetin has been demonstrated to suppress the functioning of drug efflux pumps such P-glycoprotein (P-gp), which contribute to multidrug resistance in cancer cells, in addition to its effects on mitochondrial function and the development of anti-apoptotic proteins. Quercetin raises the intracellular concentration of chemotherapeutic medicines and improves their cytotoxic effects by decreasing P-gp function (76). Overall, quercetin targets a number of processes that support cancer cells' mitochondrial drug resistance to exercise its anti-cancer actions. Modulation of mitochondrial activity, suppression of anti-apoptotic protein production, and blockage of drug efflux pumps are some of these ways. Quercetin has generated a great deal of interest as a possible adjuvant therapy for the treatment of cancer due to its wide spectrum of anti-cancer actions (77).

Sulforaphane

Cruciferous vegetables like broccoli, cauliflower, and kale contain a natural substance called sulforaphane that has been demonstrated to have anticancer characteristics. A prospective possibility for cancer treatment, sulforaphane has recently been found to be able to target the mitochondrial drug-resistance pathways in cancer cells. Through controlling energy metabolism and cell death, mitochondria play a crucial role in cancer cell survival and medication resistance. By changing cellular metabolism, lowering reactive oxygen species (ROS) levels, and inhibiting apoptotic cell death in cancer cells, mitochondria can become dysfunctional and aid in the development of chemotherapeutic resistance. Reduced sensitivity to various anticancer medications, including as cisplatin, doxorubicin, and paclitaxel, is linked to mitochondrial dysfunction. In cancer cells, sulforaphane has been demonstrated to reverse drug resistance and restore mitochondrial function. As a result of sulforaphane's activation of the Nrf2 pathway, which increases the synthesis of antioxidant enzymes and lowers ROS levels, the body produces more antioxidants. Sulforaphane's stimulation of the Nrf2 pathway can improve mitochondrial performance and lessen drug resistance in cancer cells. Sulforaphane also has the ability to control the expression of mitochondrial proteins linked to drug resistance. MRP1, an ATP-binding cassette transporter protein that contributes to drug resistance, is expressed less often when sulforaphane is present (78). The expression of the mitochondrial protein BNIP3L is also upregulated by sulforaphane, which causes mitochondrial autophagy and promotes death in cancer cells. Sulforaphane has the potential to be used in cancer treatment as a chemosensitizer, according to recent studies. Sulforaphane inhibited the Nrf2-mediated antioxidant response and decreased MRP1 expression, according to research by Chen et al. (2021), which demonstrated

that it sensitized lung cancer cells to cisplatin (79). By triggering mitochondrial autophagy through the elevation of BNIP3L expression, sulforaphane was shown to improve the susceptibility of breast cancer cells to doxorubicin in another work by Li et al. (2022) (80). Sulforaphane has demonstrated promise as a natural chemical for the treatment of cancers that have mitochondrial drug resistance pathways. The Nrf2 pathway is activated, drug-resistant mitochondrial proteins are modulated, and mitochondrial function is restored as part of the sulforaphane's mode of action. These results imply that sulforaphane may be utilized as a chemosensitizer to increase the effectiveness of traditional chemotherapy in the treatment of cancer.

Berberine

A natural isoquinoline alkaloid known as berberine has been proven to have anticancer properties against a variety of malignancies, including tumors that are drug-resistant. Alterations in mitochondrial activity are one of the processes through which cancer cells gain resistance to chemotherapy. According to reports, berberine affects cancer cells that are resistant to treatment through modifying mitochondrial activity. It has been demonstrated that berberine targets the mitochondrial pathway to cause apoptosis in cancer cells. Depolarization of the mitochondrial membrane potential has been linked to the onset of apoptosis by releasing cytochrome c into the cytoplasm and activating caspases (81). Additionally, berberine has been shown to induce autophagy, a process by which cells recycle their own components in response to stress. This is accomplished by increasing the susceptibility of cancer cells to chemotherapy by stimulating the formation of autophagosomes and lysosomes, which causes the destruction of cellular components, including damaged mitochondria. Additionally, berberine has been shown to control the production of a number of proteins essential for mitochondrial function. It has been demonstrated, for instance, that it inhibits the expression of the mitochondrial ATP synthase subunits and, which results in a reduction in ATP production (82). Additionally, it has been demonstrated that berberine stimulates AMP-activated protein kinase (AMPK), an essential regulator of cellular energy metabolism. Protein synthesis is inhibited and autophagy is induced when AMPK is activated (83). This is because mTOR signaling is inhibited. Additionally, it has been shown that berberine inhibits the production of the anti-apoptotic protein Bcl-2, known to suppress mitochondrial apoptosis and make cancer cells more susceptible to chemotherapy (84-85). The regulation of mitochondrial activity in cancer cells that are resistant to treatment is how berberine has been proven to exercise its anticancer effects. It triggers autophagy and apoptosis and modifies the expression of several proteins vital to mitochondrial function. As a result, berberine has

potential therapeutic uses in drug-resistant malignancies as a chemotherapy sensitizer.

Lycopene

A carotenoid phytochemical called lycopene is present in foods including tomatoes, watermelons, and grapefruits. According to studies, lycopene has strong anti-oxidant qualities and may help prevent or treat a number of ailments, including cancer. Targeting cancer cells' mitochondrial drug-resistance pathways is one way lycopene may work. Drug resistance in cancer cells frequently develops via a process known as mitochondrial drug resistance. Anti-apoptotic proteins like Bcl-2, which block the release of cytochrome c from the mitochondria and stop the activation of caspase-dependent apoptotic pathways, are overexpressed during this process. It has been demonstrated that lycopene targets mitochondrial drug resistance by preventing Bcl-2 and other anti-apoptotic proteins from being expressed in cancer cells. The expression of Bcl-2 and other anti-apoptotic proteins was shown to be significantly reduced by lycopene treatment in research on prostate cancer cells, which enhanced mitochondrial permeability and activated caspase-dependent apoptotic pathways (86). By triggering the caspase-dependent pathway and suppressing the expression of Bcl-2 and other anti-apoptotic proteins, lycopene therapy was shown in another study to cause apoptosis in human cervical cancer cells (87). Lycopene has been demonstrated to have other anti-cancer effects, including the ability to suppress cell growth, cause cell cycle arrest, and decrease inflammation, in addition to its function in addressing mitochondrial drug resistance (88). Overall, the data points to lycopene's potential as a therapeutic agent for the treatment of cancer, especially when it comes to focusing on mechanisms of mitochondrial drug resistance. To completely understand the processes behind lycopene's anti-cancer benefits and to assess its effectiveness and safety in clinical trials, further study is necessary.

Genistein

Studies have demonstrated that the soy isoflavone genistein can overcome medication resistance in cancer cells, which has been related to mitochondrial malfunction. Breast, prostate, lung, and colon cancers are only a few of the tumors for which genistein has been reported to be helpful. Researchers have shown a significant deal of interest in the mechanism by which genistein overcomes drug resistance in cancer cells in this context (89). It has been demonstrated that genistein targets multiple molecular pathways, including the mitochondrial pathway, that are important in cancer cell survival and proliferation. Apoptosis, also known as programmed cell death, is a process by which the body gets rid of defective or damaged cells, and mitochondria play a critical part in

controlling it. This pathway is frequently damaged in cancer cells, which increases their resistance to chemotherapy treatments (90). Modulating the activity of the mitochondrial permeability transition pore (mPTP) is one of the primary ways that genistein overcomes mitochondrial drug resistance in cancer cells. A channel called the mPTP controls how ions and other small molecules are transported through the inner mitochondrial membrane. Its dysregulation has been linked to drug resistance in cancer cells and it has been demonstrated to be involved in the control of apoptosis (91). By controlling the expression of many proteins crucial to the mPTP's operation, genistein has been discovered to modify the mPTP's activity. For instance, it has been demonstrated that genistein increases the production of the protein cyclophilin D (CypD), which encourages the opening of the mPTP and causes apoptosis. Additionally, it reduces the production of Bcl-2, a protein that blocks the opening of the mPTP to limit apoptosis (92). Genistein has been demonstrated to target other mitochondrial proteins related to drug resistance in addition to altering the mPTP. For instance, it has been discovered to disrupt the mitochondrial respiratory chain's function, increasing the formation of reactive oxygen species (ROS). ROS are very reactive chemicals that have the ability to kill cancer cells by harming their DNA, proteins, and lipids (93). Overall, the regulation of several molecular pathways is part of the complicated process by which genistein overcomes cancer cells' mitochondrial drug resistance. However, research indicates that the primary methods through which genistein might cause apoptosis in drug-resistant cancer cells are through its capacity to target the mPTP and control ROS generation.

Kaempferol

Natural flavonoid kaempferol, which is present in many plants, has been demonstrated to have anti-cancer activities and to circumvent drug resistance in cancer cells via a number of pathways (94). The regulation of the mitochondrial membrane potential (MMP) and the inhibition of drug efflux from cancer cells are two ways that kaempferol works to overcome mitochondrial drug resistance. The transport of numerous chemotherapeutic medicines out of cancer cells is carried out by adenosine triphosphate (ATP)-binding cassette (ABC) transporters, which also facilitate the efflux of medications from cancer cells. It has been demonstrated that kaempferol inhibits the function of ABC transporters, preventing medications from being effluxed from cancer cells and raising the concentration of pharmaceuticals inside cells, enhancing cytotoxicity (95). Additionally, it has been demonstrated that kaempferol causes cancer cells to undergo apoptosis (programmed cell death) by activating the caspase pathway and reducing the expression of the anti-apoptotic B-cell lymphoma 2

(Bcl-2) protein. Since cancer cells are defined by the inhibition of apoptosis, which results in unchecked proliferation and survival, apoptosis activation is crucial for the therapy of cancer (96). Inhibiting the activity of mitochondrial respiratory chain complexes and boosting the generation of reactive oxygen species (ROS), kaempferol also controls mitochondrial function. Cancer cells typically exhibit mitochondrial malfunction and altered redox homeostasis, and kaempferol's regulation of mitochondrial activity can result in the selective destruction of cancer cells (97). Additionally, it has been demonstrated that kaempferol increases the intracellular drug concentration and boosts the cytotoxic effects of chemotherapy drugs, making cancer cells more susceptible to chemotherapy. In cancer cells that are resistant to chemotherapy, this process is particularly important, and kaempferol can break down this resistance by boosting the effectiveness of chemotherapy (98). Kaempferol has been shown to have the ability to combat medication resistance in a number of cancer types, including breast cancer, lung cancer, ovarian cancer, and pancreatic cancer, in recent research. However, further research is needed to clarify the precise mechanisms of action of kaempferol in various cancer types and to create kaempferol-based therapy approaches.

Naringenin

A flavonoid substance called naringenin is present in citrus fruits like grapefruit and oranges. Numerous biological activities, such as antioxidant, anti-inflammatory, and anticancer effects, have been found for it. Naringenin may be able to break through drug resistance in cancer cells, particularly due to its impact on mitochondrial activity, according to recent research. One frequent mechanism underpinning medication resistance in cancer cells is mitochondrial malfunction. Changes in mitochondrial metabolism, oxidative stress, and ATP generation are its defining characteristics, and they all work together to enhance survival and confer resistance to chemotherapy. Naringenin has been demonstrated to target the mitochondria in cancer cells, reducing medication resistance and enhancing therapeutic results. Zhao et al.'s (2021) research looked at how naringenin affected lung cancer cells' treatment resistance. The results of the study showed that naringenin therapy reduced drug resistance, which was connected to improved mitochondrial function and reduced oxidative stress. By improving mitochondrial activity and decreasing drug resistance in cancer cells, the scientists suggested that naringenin may increase the effectiveness of chemotherapy (99). Kim et al.'s (2020) research looked at how naringenin affected breast cancer cells' treatment resistance. According to the study, naringenin treatment made cancer cells more susceptible to chemotherapy, which was linked to both an increase in reactive oxygen species (ROS) generation and a reduction in mitochondrial

respiration. By altering mitochondrial activity and boosting ROS generation, the scientists hypothesized that naringenin would be able to break through treatment resistance in breast cancer cells (100). Finally, it has been demonstrated that naringenin may overcome medication resistance in cancer cells by concentrating on mitochondrial activity. It has been discovered that the substance improves mitochondrial function and lowers oxidative stress, which reduces medication resistance and improves therapeutic results. The molecular processes underpinning naringenin's impacts on mitochondrial function and drug resistance in cancer cells require more study to be completely understood.

Apigenin

A flavone substance called apigenin is present in many plants, such as celery, parsley, and chamomile. Apigenin has been proven in studies to have anticancer effects and to be able to break through cancer cells' drug resistance to mitochondrial agents. Cancer cells can become resistant to chemotherapeutic treatments through a mechanism known as mitochondrial drug resistance. We will talk about how apigenin overcomes cancer's mitochondrial drug resistance in this response. Drug-resistant cancer cells have an overexpression of the drug efflux pump P-gp. It is in charge of pushing chemotherapy medications out of cancer cells, which reduces drug buildup and causes chemotherapy resistance. In drug-resistant cancer cells, apigenin suppresses P-gp expression and function, increasing drug accumulation and enhancing chemotherapy effectiveness (101). The apoptosis process—by which damaged or diseased cells are destroyed—is regulated by Bcl-2 family proteins. By upregulating anti-apoptotic Bcl-2 family proteins, which prevent apoptosis and support cell survival, certain cancer cells develop resistance to chemotherapy. Apigenin inhibits Bcl-2 family proteins, increasing apoptosis and enhancing the effectiveness of chemotherapy (102). An energy-sensing kinase called AMPK controls cellular survival and metabolism. Chemotherapy resistance in cancer cells results from changing metabolic pathways and enhancing cell survival. Drug-resistant cancer cells undergo metabolic reprogramming and improved susceptibility to chemotherapy as a result of apigenin activating AMPK (103). In order for cells to survive and function properly, mitochondria are essential. By modifying mitochondrial activity, cancer cells become resistant to chemotherapy, which results in less drug accumulation and higher cell survival. Apigenin improves chemotherapy effectiveness by modulating mitochondrial function by controlling mitochondrial biogenesis, membrane potential, and reactive oxygen species (ROS) generation (104).

Coumarin

Numerous plants contain the natural substance coumarin, which is well recognized for its wide range of biological effects. Recent studies have looked at how coumarin and its derivatives may help fight cancer drug resistance mechanisms, concentrating in particular on how they may affect mitochondrial function (105). Cellular energy generation, apoptosis control, and redox balance maintenance are all greatly aided by mitochondria. It has been suggested that dysfunctional mitochondria contribute to the emergence of drug resistance in cancer cells (106). Drug resistance in mitochondria is caused by a number of processes, including decreased mitochondrial apoptosis, changed metabolism, and more mutations in the mtDNA. A possible method to combat cancer medication resistance is to target mitochondrial activity. Recent research has demonstrated that coumarin and its derivatives have strong modulatory effects on the mitochondria, making them prospective options for treating cancer treatment resistance (107). It has been discovered that coumarin chemicals control mitochondrial respiration, restore the potential of the mitochondrial membrane, and prevent the production of ATP in the mitochondria. These processes have been linked to reverse drug resistance and sensitizing cancer cells to chemotherapeutic medicines. Apoptosis in the mitochondria is a crucial step in the destruction of cancer cells. Cancer cells that are resistant to drugs frequently have dysregulated mitochondrial apoptosis, which prevents them from dying. By altering the expression of proteins associated with apoptosis, such as the Bcl-2 family of proteins and caspases, coumarin has been demonstrated to encourage mitochondrial death (108). Coumarin can improve the effectiveness of chemotherapeutic medicines by reestablishing mitochondrial apoptosis. A distinguishing feature of cancer cells is altered mitochondrial metabolism, which includes increased glycolysis and decreased oxidative phosphorylation. According to certain studies, coumarin chemicals inhibit glycolysis and restore oxidative phosphorylation to influence mitochondrial metabolism. This metabolic reprogramming can enhance the effectiveness of chemotherapy by making drug-resistant cancer cells susceptible to it. Drug resistance in cancer cells has been linked to an accumulation of mtDNA mutations. Recent research has shown that coumarin has protective properties against mtDNA damage brought on by chemotherapy treatments. Coumarin can help avoid the development of drug resistance by maintaining the integrity of mtDNA and increase the efficacy of anticancer therapies (109).

Rutin

Rutin, a naturally occurring flavonoid present in a variety of fruits and vegetables, has drawn substantial interest in cancer research because of its possible role

in overcoming mitochondrial drug resistance pathways. By modifying mitochondrial activities, which results in decreased drug absorption and greater drug efflux, cancer cells can resist the effects of chemotherapy medications. This phenomenon is known as mitochondrial drug resistance. The development of medication resistance is facilitated by this process, which makes treating cancer more difficult. Rutin's ability to reduce mitochondrial drug resistance in various cancers has been looked at in a number of recent research. The emergence of medication resistance is strongly influenced by mitochondrial malfunction. Rutin has been discovered to alter the activity of the mitochondria, returning it to its natural physiological condition and reversing drug resistance (110). Rutin decreases levels of reactive oxygen species (ROS) while increasing mitochondrial biogenesis, respiration, and ATP generation. These outcomes enhance drug sensitivity in cancer cells and aid in the restoration of regular mitochondrial activities. Reduced intracellular drug concentrations and consequent resistance are caused by drug efflux pumps like P-glycoprotein (P-gp), which actively transport chemotherapy medicines out of cancer cells. Rutin has been demonstrated to inhibit P-gp and other drug efflux pumps, boosting intracellular drug accumulation and reducing resistance (111). Rutin's suppression of drug efflux pumps enhance the effectiveness of chemotherapy medicines. Apoptosis is a kind of programmed cell death that gets rid of cancer cells, and mitochondria are crucial to this process. One hallmark of cancer cells that are resistant to treatment is resistance to apoptosis. By altering the production of pro- and anti-apoptotic proteins, rutin has been identified to control apoptotic pathways. Drug-resistant cancer cells become more susceptible to apoptotic signals because it encourages the activation of caspases, which are important apoptosis mediators. It also suppresses anti-apoptotic proteins. Rutin has shown synergistic effects with a number of chemotherapeutic drugs, increasing their cytotoxicity against cancer cells that have developed drug resistance (112). Rutin has been demonstrated to enhance drug absorption, boost ROS production, trigger apoptosis, and decrease cell growth in combination treatment with chemotherapeutic medicines. These beneficial interactions offer hope for reducing mitochondrial drug resistance and enhancing chemotherapeutic effectiveness (113). In conclusion, Rutin has enormous promise for overcoming the mechanisms of mitochondrial drug resistance in cancer. It is a prospective option for future therapeutic treatments due to its capacity to affect mitochondrial activity, prevent drug efflux pumps, control apoptotic pathways, and work in concert with chemotherapy drugs. However, further study is required to clarify the underlying molecular pathways and enhance its therapeutic use in the treatment of cancer.

Conclusion and Future Perspectives

Phytochemicals are organic substances that are naturally present in plants and have been demonstrated to offer a number of health advantages, including anti-cancer capabilities. One of the ways that phytochemicals can exert their anti-cancer effects is by altering the activity of cancer cells' mitochondrial drug-resistance mechanisms. The energy-producing organelles in cells called mitochondria are essential for cellular metabolism, growth, and survival. Cancer cells often exhibit altered mitochondrial function, which can contribute to drug resistance and tumor progression. Phytochemicals can change the function of mitochondrial proteins and enzymes, causing disruption of cancer cells' drug-resistance processes. As an illustration, it has been demonstrated that some phytochemicals can impede the mitochondrial respiratory chain's function, lowering the synthesis of ATP (the cell's energy currency), and causing cell death in cancer cells. Some phytochemicals can also enhance the amount of reactive oxygen species (ROS) produced by cancer cells. ROS are harmful byproducts of cellular metabolism that can damage biological elements, including DNA, and ultimately cause cell death. In drug-resistant cancer cells that have evolved defenses against ROS, phytochemicals can cause cell death by raising ROS levels. Overall, an increasing collection of preclinical and clinical data supports the hypothesis that phytochemicals might modify the activity of cancer cells' mitochondrial drug-resistance systems. To completely comprehend the processes by which phytochemicals exert their anti-cancer benefits, however, and to determine the most potent phytochemicals for use in treating cancer, additional study is required.

Plant-based substances known as phytochemicals have been demonstrated to offer a number of health advantages, including the capacity to change the activity of cancer cells' mitochondrial drug-resistance pathways. The energy centers of the cell, mitochondria are essential for metabolism and energy synthesis. As a result of malfunctioning mitochondria, cancer therapies may be less effective and drug resistance may grow. Here are some key points regarding the future perspective of phytochemicals in altering cancer cell mitochondrial drug-resistance mechanisms:

1. Mitochondria are essential for cancer cell survival and chemotherapy resistance. Cancer cells can acquire a resistance to the cytotoxic effects of anticancer medications by changing the mitochondrial activity and metabolism.
2. Phytochemicals are bioactive substances that are present in plants and have a number of positive health effects. Numerous phytochemicals are being researched as

possible medicines to combat drug resistance since they have shown anticancer effects.

3. Phytochemicals can target drug resistance-related mitochondrial pathways. They have the ability to alter mitochondrial membrane potential, boost apoptotic signalling, reduce ATP generation, and damage mitochondrial DNA integrity, making cancer cells more susceptible to chemotherapy.
4. Some phytochemicals influence the levels of ROS in cancer cells to produce their anticancer effects. ROS can affect medication resistance and are crucial for mitochondrial function. Phytochemicals may either boost the production of ROS to kill cells or scavenge too much ROS to keep the mitochondria healthy.
5. Phytochemicals may influence the mitochondrial transporters involved in drug absorption and efflux to influence drug resistance. These transporters can increase resistance and control the intracellular concentration of anticancer medications. To overcome resistance, phytochemicals can block drug efflux transporters or improve drug accumulation within mitochondria.
6. By having a synergistic impact, phytochemicals can increase the effectiveness of chemotherapy medications. Drug resistance can be overcome and treatment results can be improved by combining phytochemicals with standard anticancer medications.
7. Fruits, vegetables, herbs, and conventionally used medicinal plants are only a few examples of the natural sources from which phytochemicals can be obtained. These natural sources offer a wide range of bioactive substances that might be researched for their potential anticancer effects.
8. The potential role of phytochemicals in modifying the drug-resistance pathways in cancer cells is consistent with the idea of customized treatment. Phytochemicals can be specifically formulated to target and overcome medication resistance on an individual basis by comprehending the distinct mitochondrial changes and drug resistance pathways in different individuals.
9. Clinical applications of phytochemical research have the potential to enhance cancer treatment results. Creating phytochemical-based treatments or combining them with standard chemotherapy can offer fresh ways to combat drug resistance and improve patient survival.

Overall, the future perspective of phytochemicals in altering cancer cell mitochondrial drug-resistance mechanisms is promising, but more research is needed to fully understand their potential benefits and

limitations in cancer treatment.

Declarations

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